

EXHIBIT B

Part 2

"Investigations of an unexplained discrepancy and failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same product and other drug products that may have been associated with the specific failure or discrepancy.

"We discussed the failure of Quality Assurance to document and complete investigations at the time of occurrence with Ms. Lambridis. A list of Quality Assurance Investigations from 9/07 to the present by product was requested (Exh. 6). The list revealed that the investigations into out of specification results (as documented in FDA-483 observations 2, 3, and 4), remained open. Xxxx Xxxx was introduced during the inspection. She joined the company in 1/08 and will oversee Quality Investigations, CAPAs, and complaints for the New Jersey sites. I, Investigator McCaffery asked Ms. Sherwani how she planned to remediate the backlog of QA investigations in the absence of adequate staffing and systems. She explained that she was trying to work closely with Quality Control to understand the laboratory findings and plans to increase her group to respond to the backlog. Ms. Lambridis confirmed that they needed additional resources and were hiring, but were not fully staffed. We discussed the need to address out of specification product in a timely manner. On several occasions during the inspection, Ms. Lambridis stated that she needed time to stop and review the product issues. Due to the lack of documentation and completions of the QA investigations, the investigative information was not compiled reviewed or approved. In some cases, Ms. Lambridis had not been made aware of significant quality issues by local quality personnel. (Ref 14 p. 54-55)

"Specifically,

"Although xxxxxx dated 1/25/08, for double thick Digoxin tablets lot# 70924A1 failed to establish a root cause for the defective tablets, the investigation was not expanded to evaluate all finished product lots or strengths of Digoxin Tablets. At the time of inspection there were approximately lots of Digoxin Tablets. At the time of inspection there were approximately xx lots of Digoxin Tablets 0.125 mg and lots Digoxin Tablets 0.250 mg on the market within expiry. (Ref 14 p. 55)

"A Quality Assurance investigation xxx dated 1/25/08, for Digitalis "double thick" tablets, lot# 70924A1 failed to establish a root cause for the defective tablets (Exh. 2a1) as documented in FDA 493 observations 2a. The product was visually inspected to remove the "double thick" tablets and was subsequently released to the market (Exh. 2a3 p.6). The product continued to be manufactured with no assurance that other batches had been or would be impacted by the issue. There was no health hazard evaluation conducted to determine the potential patient impact upon taking a "double thick" Digoxin Tablet. There were xxx of Digoxin Tablets, 0.125mg and xxx lots of Digoxin Tablets, 0.250mg which are manufactured on the same equipment, with the same operators and raw material supply. The QA investigation was signed by the Director of Quality Assurance, who noted in the impact analysis, "The deviation is considered an isolated incident; therefore no other batches are impacted." (Exh. 2a1 p. 2) Ms. Lambridis notified us on 4/17/08 that the firm was voluntarily recalling 10t# 70924A2 (repack of lot# 70924A1 following visual inspection). We discussed the failure to evaluate other batches due to the lack of root cause in the investigation and the discrepancies between the investigational theories. We Office of Compliance during the inspection due to the potential risk of "double thick" tablets, Robert Wessman, CEO was contacted by New Jersey District on 4/24/08. (Ref 14 p. 55)

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"OBSERVATION 7 (Ref 14 p. 58)

"An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application. (Ref 14 p. 58)

"A list of the NDA Field Alerts filed at the time of inspection was provided as Exh. 7. An updated list of all Field Alert Reports received during and after the inspection by New Jersey "District is provided as (Att). Ms. Lambridis discussed the firm's historical hesitation to notify FDA of potential product issues. She stated that she joined the company and began to evaluate some of the out of specification stability results, she prompted the filing of the Field Alerts. She stated that since the hiring of Misbah Sherwani, Senior Manager Quality and Investigation, they have been filing reports on time. Ms. Lambridis stated that Field Alerts will be filed within three days of the initial findings as per regulation. (Ref 14 p. 58)

"Specifically, alert reports for the following products with confirmed stability out of specification results were not within three working days of receipt of information. SECTION DELETED (Ref 14 p. 58)

"OBSERVATION 8 (Ref 14 p. 60)

"Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications. Specifically, Quality Assurance investigations are not documented, at the time of occurrence and are not completed in a timely manner as required by xxx Deviations, dated 11/3/06. For examples, SECTION DELETED. There were no documented investigative steps to determine the root cause, no discussion of the risk associated with the OOS results and no evaluation of the lots on the market. During the inspection, a new draft xxxx was provided which included xxxx lots which noted that "all in date marketed product will be recalled. New Jersey Recall coordinator was notified on 4/9/08 of the voluntary recall. (Ref 14 p. 60)

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"We discussed numerous examples of undocumented and untimely Quality Assurance investigations with Ms. Lambridis. A summary of the open and closed QA investigations by was provided (Exh. 5f2). Ms. Lambridis stated that was aware of issue; however she did not have the staffing to support the large influx of investigations. We noted our concern about the failure to respond to product quality issues in a timely manner to both Ms. Lambridis and Ms. Eyjolfssdottir, the U.S. and Global heads of Quality, respectively. At the exit meeting, Mr. Wessman provided a commitment to supply resources to complete the backlog of open Quality assurance investigations. His commitment was also provided in writing a letter dated 5/20/08. During the inspection we also discussed the need to develop sustainable Quality Systems to facilitate and appropriate responses to product quality issues. (Ref 14 p. 64)

"OBSERVATION 9 (Ref 14 p. 65)

"Written production and process control procedures are not followed in the execution of production and process control functions. (Ref 14 p. 65)

"Specifically, xxxxxx, dated 11/3/06 required completion of investigations with in xx working days. If an extension is needed, a memo to file describing the progress and the target completion date is required. Numerous Quality assurance investigations remained open during the inspection including investigations of Carisoprodol, Aspirin, and Codeine Phosphate Tablets, USP, lot# 60484A1 initiated. SECTION DELETED There was also no risk assessment for the potential impact of the product on the market, despite the delay. SECTION DELETED (Ref 14 p. 65-66)

"The failure of the Quality Unit to follow the SOP and meet timeframes resulted in a lack of response to product quality issues. We discussed the incomplete QA investigations throughout the inspection with Ms. Lambridis. At the exit meeting, Mr. Wessman stated that as part of the firm's corrective actions, resources would be provided to complete, review and approve the backlog of QA investigations (Exh. 5f2). The commitment for completion of QA investigations

was also provided in a letter from Mr. Wessman, dated 5/20/08 (Exh. 16).SECTION DELETED (Ref 14 p. 66)

"Xxxxxx with the FDA, dated 10/31/07 (Exh. 9c1) Section 5.4.1 states, "Within three working days of obtaining the information, the Site, Head of Quality or designee must file a Field Alert Form with the District Office that is responsible for the manufacturing facility." The procedure requires filing of confirmed or unconfirmed issues such as stability failures or any other significant chemical, physical or other change in a distributed product. FDA-483 observation 7-a-d documents the failures of the firm to follow xxxxxxxx. Field alerts were not filed as per procedure for [multiple products].SECTION DELETED (Ref 14 p. 67)

"OBSERVATION 10 (Ref 14 p. 68)

"Changes to written procedures are not reviewed and approved by the quality control unit. (Ref 14 p. 68)

"Specifically, changes are not all captured within the formal control system that is documented in Work Orders are not reviewed and approved by the Quality Unit. In addition, documentation of justification for changes within the change control is reviewed by xxxxxxxxxxxxxx this justification is lacking in detail with respect to product quality. For example: (Ref 14 p. 68)

"Work Order Forms, which are not reviewed and approved by the Quality Unit are issued when transferring equipment from one facility to another and when equipment is not functioning properly. For example: SECTION DELETED Quality Unit did not review and approve xxxxxxxxxxxxxx issued on 12/27/07 and 2/12/08; respectively, to document the transfer of the xxxxxxxx used for the production of Digoxin Tablets, from the Little Falls, NJ manufacturing to the Riverview, NJ. No formal qualification was conducted following the movement of the blender from one site to another. (Ref 14 p. 68)

"Work Order #1001 was issued on 12/27/07 to document the transfer of the xxxxxxxxxxxxxx from the Little Falls manufacturing facility to the Riverview Drive manufacturing facility (Exh. 10ai1) xxxxxxxxxxxxxx is used in the production of Digoxin Tablets as shown the Process Validation Report for Digoxin 0.125 mg (Exh. 10ai2) and the Equipment Usage and Cleaning Log for the xxxxxxxxxxxxxx (Exh. 10ai3). The work order (#1001) was requested by the Director of Operations at Little Falls; the work was performed by Maintenance personnel, and the Work Order was approved by the Director of Operations at Little Falls. The Quality Unit did not review or approve the movement of this equipment. In addition, no formal qualification was conducted following the movement of the blender from one site to the other. A second Work Order #1039, was issued on 21/21/08 to, again document the transfer the xxxxxxxxxxxxxx (used for the production of Digoxin Tablets) from the Little Falls manufacturing site to the Riverview Drive manufacturing site (Exh. 10ai4). The work order was requested by the Manager of Manufacturing at Little Falls; the work was performed by Maintenance personnel, and the Work Order was approved by the Director of Manufacturing (Little Falls and Riverview). The Quality did not review or approve the movement of this equipment and no formal qualification was conducted following the movement of the blender from one site to the other. (Ref 14 p. 68-69)

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"OBSERVATION 11 (Ref 14 p. 72)

"Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. (Ref 14 p. 72)

"Specifically, Investigations of Deviation Reports require a review by Quality Assurance, an approval by Regulatory Affairs/ Quality Compliance and an approval of product disposition by

the Head of Quality Assurance. On multiple occasions, these three signatories were completed by the same individual. For example: (Ref 14 p. 72)

"XXXXXX regarding double thick xxxx was signed by the Director of Quality Assurance under the sections designated for Quality Assurance, Regulatory Affairs/quality Compliance and the Head of Quality Assurance. (Ref 14 p. 72)

"The Director of Quality assurance signed under the Sections designated for Quality Assurance, Regulatory Affairs/Quality Compliance and the Head of Quality assurance in the QA investigation xxx regarding "double thick" Digoxin Tablets 0.125 mg, lot# 70924A1/A2 (Exh. 2a1). Refer to FDA-483 observation 2a for details regarding this lot. (Ref 14 p. 72)

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"GENERAL DISCUSSION WITH MANAGEMENT (Ref 14 p. 74)

"Discussions with management were held throughout the inspection due to the numerous inspectional findings. We, Investigators Zielny and McCaffery, informed Phyllis Lambridis, VP U.S. Quality and Compliance and xxxxxxxxx of our findings at the site as they were identified on a daily basis. Two additional meetings with the firm's upper management were conducted during the inspection. See "MEETINGS WITH MANAGEMENT" section. (Ref 14 p. 74)

"At the exit meeting on 5120108 discussions with management were held prior to the issuance of the FDA-483, Inspectional Observations. Following the discussions with management, the FDA-483, Inspectional Observations was issued to Mr. Robert Wessman, CEO Actavis Group. Although the firm made commitments for corrective actions in response to our findings during the inspection, there are several areas that remain unaddressed. There are a large number of product lots that were manufactured, tested and released by the same Quality System that failed to document, evaluate and address the product quality issues: identified by representative examples in the FDA-483, Inspectional Observations, dated 5/20/08. The inspection did not cover and products, processes, or methods and only covered one of six systems at the facility. The failure of the Quality System and the concern about the quality of other products for which we did not do in depth evaluations was discussed with Mr. Wessman, Mr. Signor Oli Olafsson, Mr. Rope and Ms. Lambridis at the exit meeting. The products manufactured under that failed Quality System remain in question and are both on the market and in the xxxxxx. (Ref 14 p. 75)

"Prior to the exit meeting we had requested a list of all product lots reviewed by the consultants and released by the Quality Unit. At the exit meeting, Ms. Lambridis provided a list of and indicated that additional lots had been reviewed and released since the consultants had started on approximately 4/25/08. We discussed the failure to provide the recall documentation to the District Office and the delays in obtaining documents and other information during the inspection, but the ability to provide resources to review and release product to the market in such a short period of time. We expressed our concerns regarding the adequacy of the "risk review" the firm and their consultants conducted for these products xxx noted that approximately xxx had been released after review by the firm's consultants, although several unresolved product quality issues related to these products were documented on the FDA-483. A list of the lots released follow in PAREXEL review was provided as Exh. 38. We were no additional batches that had also been released for a total of xxxxxxx. (Ref 14 p. 75)

"We acknowledged the commitment to voluntarily remove the product from the market but noted the Quality Unit's inability to identify and correct problems independently. Ms. Lambridis stated that although resources were needed, they had not been successful in hiring as quickly as they had hoped. We discussed the need not only for additional resources, but for timely science based on the issues that we discussed. (Ref 14 p. 75)

"At the exit meeting we stated to Robert Wessman; CEO that none of the final recall letters or final recall packages had been to New Jersey District as 5/20/08 at the meeting, despite our notification to Ms. Lambridis during the inspection that the recall information was needed within f notification of the recall. The recall packages had been promised to the New Jersey District Recall Coordinator for two weeks prior to the exit meeting. Ms. Lambridis stated that four of the recall packages would be provided i9 the District on 512110S and that remaining recall packages from the first group of products recalled would be provided to the District by 5/23/08. (Ref 14 p. 75)

"Mr. Wessman gave a verbal commitment at the exit meeting to discontinue the release of any additional batches until further discussions are held with the District; improve the infrastructure of the firm's quality system; provide the district with a timeframe for completing the "risk reviews" of the products remaining on the market; aggressively work to close the many open investigations; and resume manufacturing one process at a time. He provided 'a written commitment later that day confirming this commitment. (Ref 14 p. 75)

"ADDITIONAL INFORMATION (Ref 14 p. 76)

"Mr. Wessman committed to temporarily discontinuing the release of lots based on a paper review conducted by the consultants for the products in the distribution centers, he did not commit to removal of the other lots that remain on the market which were manufactured, analyzed and released by a failed Quality System. A comprehensive list of products remaining on the market was requested at the exit meeting and provided by Ms. Lambridis after the inspection (Exh. 39). (Ref 14 p. 76)

"The responses to all findings were reactive and not pro-active. At the initiation of the inspection, the firm had more than xxxxxx for which confirmed stability failures were documented and confirmed by their laboratory. The Quality Unit had not responded to any of the failures to remove the out of specification product from the marketplace. No recalls were initiated in response to the failures at the initiation of the inspection on xxxx. The recalls were initiated after extensive discussions of the violations and a request for interstate documentation for the out of specification stability lots. Additional recalls were initiated based on' our continued findings. The findings of consultants who were hired as of the firm's corrective action We acknowledged the commitment to voluntarily remove the product from the market but noted the Quality Unit's inability to identify and problems independently. Ms. Lambridis stated that although resources were needed, they had not been successful at hiring as quickly as they had hoped. We discussed the need not only for additional resources, but for timely science based responses to issues' identified. (Ref 14 p. 76)

"We were notified of the initial recalls on 4/4/08; on 5/2/07 the remained on the market. We questioned the date that the recall letters were sent. Ms. Lambridis contacted Capital sent. Site stated that Actavis was delayed in providing the letters and therefore delayed Capital Recall's mailing. We were notified 5/7/08, approximately one month after the commitment to recall products that the recall letters were sent At the exit meeting we stated to Robert Wessman, CEO that none of the final recall lett7rs or final recall packages had been provided to New Jersey District as at meeting, our notification to Ms. Lambridis that the was needed within xxxx of notification of recall. We also discussed the use of resources to attempt to release additional products when the still had not been provided to the District and the Quality System failures recall were promised to the New for two weeks to the exit meeting. Ms. stated that four of the recall packages would be provided to the District on 512 HOB and that the remaining recall

packages from the first group of products recalled would be provided to the District by 5/23/08. (Ref 14 p. 76-77)

"Prior to the exit meeting we requested a list of all product lots reviewed by the consultants and released by the Quality Unit, Ms. Lambridis provided a list of xxxxx (Exh. 38) and indicated that additional lots had been reviewed and released. We discussed the failure to the recall documentation to the District Office but the ability to provide resources to release product to the market Mr. Wessman gave a verbal commitment at the exit meeting to discontinue the release of any additional batches further discussions are held with the District. He provided a written commitment later that day confirming his commitment. (Ref 14 p. 77)

"We requested interstate documentation for xxxxxxxx which had documented cGMP violations. We requested the information on 4/17/08 and provided additional product specific requests on 4/22/08. On 5/15/08, when the affidavits were issued, there were outstanding shipping documents from the original request. Daniel Bitler, Director of Quality Assurance stated that shipping is not area of his responsibility and asked us what we wanted him to do if he could not obtain the records that we requested. We explained that custody and conditions under which the active pharmaceutical ingredients were held, should be assured by Quality due to their use in marketed finished products. We stated that we would collect the documentation which was available for inspection and note any missing documents in the affidavits (FDA 463a)." (Ref 14 p. 76)

COMMENT: Summary of inspection observations on the manufacturing, analytical, and quality systems that resulted in the market distribution of multiple batches of Digitek (digoxin) Tablets in which there were likely double-thick tablets that may have been suprapotent for digoxin. No analytical analysis was conducted to determine the dose of active moiety of digoxin in each double-thick tablet and no documented risk assessment of the distributed batches. In addition, the FDA inspectors document that there were "no risk assessments or routine health hazard assessments were conducted on an ongoing bases over a period of several years, including the period covered by the recall of the double-thick Digitek® (digoxin) Tablets and most likely over the entire period during which double-thick Digitek® (digoxin) Tablets were observed (i.e., since 2004). The only health hazard assessment provided for review was dated April 18, 2008 and was prepared in conjunction with the Digitek® (digoxin) Tablets. However, the health hazard assessment of April 18, 2008 does refer to a company internal document with an aggregate review of the safety data on Digitek® (digoxin) Tablets. Based upon US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events with Digitek® (digoxin) Tablets for the period of January 1, 2005 to March 31, 2008, which does not include the entire period during which double-thick Digitek® (digoxin) Tablets were observed. Eleven (11) adverse events were included in this review, and a pattern of events were not identified for this product related or unrelated to known adverse events. However, this US Actavis Medical Affairs' internal review was not reviewed in detail in the health hazard assessment, nor was it provided for review as part of this evaluation to allow independent confirmation of the conclusions. It is my opinion based on the evidence provided that there was no adequate system or business process to ensure communication between Product Complaints and Drug safety and to ensure real-time health hazard assessments were performed for all product complaints. In my opinion, an inadequate system for real-time health hazard assessments, either in process definition or in implementation, was a significant factor in the inadequate safety signal detection and inadequate assessment of the need to recall distributed batches of drug in response to product complaints.

May 28, 2009 release (Date unknown) Establishment Inspection report based on FDA-483 dated May 20, 2008 from Inspection of Actavis Elizabeth 21Apr08-21May08

SECTION DELETED

"Inspection of this generic pharmaceutical manufacturer was initiated as FACTS Assignment xxxxxxxxxxxxxxxx follow-up to Warning letter 06-NWJ-15 issued to the firm's Little Falls New Jersey location for PADE reporting was conducted. Inspectional guidance was provided through CP 73.56002, Drug Manufacturing Inspections, CP 7346.832, Pre-approval Inspections/Investigations and CP 7353.001, Enforcement of the Post-marketing Adverse Drug Experience Reporting Regulations. (Ref 15 p. 1)

SECTION DELETED

"The previous inspection of 2/21/2008 and 4/3/2008 covered. Fentanyl Transdermal complaints and is Classified VAI. The previous inspection of 12/13/2006-1/29/2007 covered the Quality, Production, Laboratory Control, and Materials Systems and was classified VAI. A GMP deficiency was noted that laboratory out-of-specifications results were not thoroughly investigated and were inconclusively attributed to analyst error. In previous PADE inspection of 8/11-14/2003 was classified NAI; however, the PADE inspection at the firm's Little Falls; New Jersey location from 1/10/2006 to 2/8/2006 revealed several deficiencies that included potential 15-day alert, cases were not submitted to FDA, serious and unexpected ADE reports were not promptly or adequately investigated; cases were not reviewed for seriousness and expectedness; and there was a lack of written procedures. The inspection was classified OAI and a Warning letter was issued for these deficiencies. (Ref 15 p. 1)

"The current inspection covered the Quality, Production, Laboratory Control and Equipment and reported to FDA, 15-day alert and periodic reports were submitted late to FDA. (Ref 15 p. 2)

SECTION DELETED

"POSTMARKETING ADVERSE DRUG EXPERIENCES (Ref 15 p. 5)

"Operations

"The Elizabeth, New Jersey site is responsible for reporting domestic and interactional - adverse drug experience, (ADE) information to FDA. The site processes approximately 100 cases a month. The Medical Affairs group relocated to Elizabeth, New Jersey from Piscataway ; New Jersey in 5/2006. There are nine people. employed in. the Medical Affairs department -, which include the Vice President Regulatory US Affairs, Director Medical Affairs, five Drug Safety /Associates and 2 Medical Affairs Coordinators (Exhibit I; page 5). Changes to the Medical Affairs department since 8/2002 are included in Exhibit 9. Exhibits 1042 are lists of products that Elizabeth, New Jersey has reporting responsibilities for Exhibit 13 is a list of products in which adverse drug information is repeated by third party. The firm uses Oracle AERS for processing and tracking reports. My review of operations included, but was not limited to 15-day alert reports, late reporting, periodic reports, deactivated cases, medical inquiries, lack of effect complaints and written procedures." (Ref 15 p. 5-6)

COMMENT: Actavis appears to be under staffed compared to comparable size companies, with no significant oversight by a Headquarters function. Decentralized pharmacovigilance operations frequently fail because of operational issues, particularly when there is not adequate centralized oversight from a headquarters function. In addition, from 1999-2006 the company had 53 approved ANDA applications, and no evidence is provided to give assurance that there was expansion of the operation infrastructure to accommodate the increased workload. However, over the 7-year period, they received 102 reports of possible adverse events and filed 48 15-day alert reports on 7 products.

"Actavis Totowa LLC Warning Letter Follow-up in 8/2006, Actavis Totowa LLC, Little Falls, New Jersey received a Warning letter for their PADE reporting system. Deficiencies cited on the Warning letter included: (Ref 15 p. 6)

- "Potential 15-day alert cases were not submitted to FDA
- "Serious and unexpected ADE reports were not promptly or adequately investigated
- "Cases were not reviewed for seriousness and expectedness; submitted cases were classified as a 15-day alert report
- "Periodic safety reports have never been submitted to FDA
- "Written procedures have not been established for follow-up 'investigations, adequate completion of MedWatch forms, maintenance of records to assure timely submission of 15-day alert reports and evaluation of adverse event data for serious outcome and event expectedness.

"Corrective actions to the Warning letter included transferring reporting responsibilities for products manufactured in Little Falls to Actavis Elizabeth. According to Sarita Thapar, Director, US Medical Affairs, the products were merged into their operations and did not require additional procedures. My review of the firm's operations included the issues cited in the Warning Letter. A similar deficiency that I observed during the inspection included unreported ADE information (refer to FDA-483 Observation 1)." (Ref 15 p. 6)

COMMENT: In previous communications with the FDA, the firm did not provide sufficient information give assurance that the FDA-483 from February 8, 2006 was followed by an aggressive compliance remediation program with root cause analysis, CAPA system, revised business processes, and a quality system with metrics to assess the effectiveness of the new systems. Repeat inspection from April to May 2008 revealed similar findings for 15-day alert reports, indicative of persistent systemic issues that may have interfered with safety signal detection.

"Waivers

"According to Dr Thapar, the firm has waivers (Exhibit 14) with the FDA for non-serious labeled events and a realignment of dates for review of periodic reports. (Ref 15 p. 6)

"Global Sites

"The firm has sites throughout the world for collecting ADE information (Exhibit 15). The collected information is then forwarded to the Denmark site. If the adverse drug, experience is associated with a drug product that has the same chemical moiety that is marketed in the US, then the information is forwarded to Elizabeth, New Jersey for evaluation, processing and submission to FDA. Dr. Thapar informed me that the Denmark site was responsible for obtaining follow-up information for the non- US sourced reports. Other responsibilities of the Denmark site are included in Exhibit 16. Dr. Thapar provided the firm's written procedures for the exchange of cases with their interactional affiliates (Exhibit 17). During the inspection, I noted that prior to 3/1/2006, ADE information was not forwarded to the firm's US site for evaluation and submission if the cases met the criteria of serious and unlabeled (refer to Observation 1). (Ref 15 p. 6)

"Literature

"Literature searches are performed weekly by the firm's site in Denmark. The firm uses Reactions Weekly for their searches, 15-day alert reports are subsequently submitted by the Elizabeth, New Jersey site. (Ref 15 p. 6)

"The firm maintains safety agreements with third party contractors. I requested and reviewed Agreements with Prosar, St. Paul, Minnesota, who reports ADE information to the FDA for Fentanyl Transdermal Patches and Mylan, who receives ADE information for Digitek® Tablets and forwards the information to Actavis Elizabeth for processing and submission to FDA. I did not observe any deficiencies." (Ref 15 p. 7)

COMMENT: Although the safety data exchange agreements are considered adequate by the FDA and are in-place and in-use, there is no information provided to give assurance of company compliance with the safety data exchange agreements.

"Patient Assistance/ Physician Samples (Ref 15 p. 7)

"The firm does not participate in any patient assistance programs, nor do they distribute physician samples for any of their products. (Ref 15 p. 7)

"Deactivated

"The firm deactivates cases from the Oracle AERS database if the case is a duplicate or a literature case that does not meet the criteria for submission. I reviewed several deactivated cases with Dr. Thapar and observed that each case included a reason for deactivation. In request of the written procedures for deactivating cases, Dr. Thapar indicated that they did not have a formal SOP; however, she provided a memo describing how the cases would be deactivated (Exhibit I 8). Xxxx discussed with Dr. Thapar and Mr. Delicato that the procedures for deactivating cases should be formalized. During the inspection, Mr. Delicate, provided a revision to SOP MA-002, Management of Suspected Adverse Drug Reaction Reports, which included deactivating cases (Exhibit 19)." (Ref 15 p. 7)

COMMENT: No information has been provided to permit assessment of the impact of inactivated cases on potential safety signal detection, aggregate analysis, or reporting compliance.

"Observations listed on form FDA-483 (Ref 15 p. 7)

"Postmarketing Experiences(Ref 15 p. 7)

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"At the closeout meeting, Mr. Delicato stated that the unreported cases from January and February 2006 would be submitted to FDA; however, Mr. Delicato informed me that they did not have a definitive answer to how far back they would go in reviewing unreported cases. He stated that they would include this information in their written response to the New Jersey District." (Ref 15 p. 8)

COMMENT: On February 8, 2006, an FDA-483 with observations of "Adverse drug experience information has not been reported to FDA. Specifically, the following adverse drug experiences or information regarding serious, unexpected adverse drug experiences were not submitted to FDA. Unsubmitted serious, unexpected 15-day alert experiences, where Amide. (the application holder or responsible party) did not submit to FDA" (Ref. 2, pp. 1-2).

The September 6, 2006 Amide response to the FDA-483 states : "Following the February inspection, we reviewed all files relating to suspected adverse drug reactions ("SADRs"), medical inquiries, and product complaints. In the process, we culled reports of 14 instances (8 ANDA and 6 DESI products) that we classified as ADEs requiring a 15-day alert report, and 94 instances that required inclusion in periodic reports. Following discussions with the Office of Drug Safety, we received permission to file a single summary ADE report, for each of the 46 applications, covering the period from the application's date of approval through March 31, 2006. Thereafter, based upon our correspondence

with the Office of Drug Safety, we filed 46 summary reports in which all events are discussed.” (Ref. 5 p.2)

An FDA Revised Warning Letter dated August 15, 2006 was written in response to the Amide response from February 28, 2006 to the FDA-483 issued on February 8, 2006. The Revised Warning letter reiterates the serious observations of noncompliance with expedited (15-day alert) reporting of serious, unexpected adverse events, and, in particular, they highlight the cases of Digitek® (digoxin) Tablets that were none submitted. The Warning Letter reiterates the serious findings regarding quality and completeness of the information on the 3500A MedWatch forms and the inadequate follow-up on serious cases. In addition, the FDA Warning Letter states “The specific violations noted in this letter are serious and may be symptomatic of underlying problems. You are responsible for investigating and determining the causes of the violations identified above and preventing recurrence of similar violations. (Ref. 4 p.3)

Thus, the FDA inspection observation from May 20, 2008 that there were still unreported cases from January and February 2006 indicates that the pharmacovigilance system and accompanying quality systems remained inadequate to ensure compliance with regulatory reporting or the requirements of the compliance remediation.

COMMENT: In addition, there are implications of the FDA observation that “Mr. Delicato stated that the unreported cases from January and February 2006 would be submitted to FDA; however, Mr. Delicato informed me that they did not have a definitive answer to how far back they would go in reviewing unreported cases. He stated that they would include this information in their written response to the New Jersey District.” The written response promised by Mr. Delicato was not included in the review package. ” No information is provided on the impact of this regulatory risk decision on potential safety signal detection on the double-thick Digitek® (digoxin) Tablets.

“OBSERVATION 2

“Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information. a. Specifically, between July 2006 and August, 2006, the firm's Denmark site forwarded approximately 200 serious and unlabeled adverse drug event cases late to the firm's Elizabeth, New Jersey site for processing and submission to FDA. Although the adverse drug, experience information was collected by the Denmark site, the date received as reported on the MedWatch form was the date received by the Elizabeth, New Jersey facility. Examples include: (Ref 15 p. 8)

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“Additionally, at least thirty (30) 15-day alert reports were submitted late to FDA between 4/2006 and 4/2008. (Ref 15 p. 9)

“Examples include:

“Case 2008AL001710, Digoxin Tablets, received on 2/7/2008 and submitted to FDA on 3/31/2008.

“Case 2008AL:001222, Amlodipine Besylate Tablets, received on 1/11/2008 and submitted to FDA on 3/7/2008.

“Case 2008AL:001104, Temazepam Capsules, received on 1/17/2008 and submitted to FDA on 3/7/2008.

“Case 2008AL:000910, Tranadol Hydrochloride Tablets, received on 1/7/2008 and submitted to FDA on 2/21/2008.” (Ref 15 p. 8)

COMMENT: This FDA inspection observation from May 20, 2008 that there were still unreported cases 15-day alert reports over 2 year after the initial FDA observation on noncompliance with expedited reporting in January and February 2006. This FDA observation indicates that the pharmacovigilance system and accompanying quality systems remained inadequate to ensure compliance with regulatory reporting or the requirements of the compliance remediation.

"Discussion with management: (Ref 15 p. 10)

"During my review of serious and unlabeled adverse drug event cases, I noted a 15-day alert report, CASE 2006AL 001965 (Exhibit 27) with an incorrect date received by manufacture on the MedWatch Form in comparison with the source data (Exhibit 27: page 10). The case was received at the Denmark site on 4/4/2006 forwarded Actavis Elizabeth in 7/24/2006 and submitted to FDA On 8/8/2006. Dr. Thapar discussed with me that from March 2006 to August 2006, Denmark sent approximately 200 cases to Actavis Elizabeth for processing and submission to FDA, Dr. Thapar explained that although the agreement for exchange began on 3/1/2006, the Denmark facility collected the cases starting on that date and began sending them to Actavis Elizabeth on 7/24/2006. For these cases, the Actavis Elizabeth started day 0 when they received the reports. A memo dated 8/31/2006 was included in the case file for 2006AL001965 and documented the Actavis decision to begin day 0 when the ADE information was received as Actavis Elizabeth for these cases (Exhibit 27; page 23). The memo also indicated that beginning on 9/15/2006 day 0 would begin when the ADE information is received at the firm's Denmark site." (Ref 15 p. 10)

COMMENT: No information is provided to give assurance of effective, centralized Headquarters oversight of regulatory compliance in the local affiliates or compliance with global workflows. There is non-compliance with timelines in global workflows with the E.U. affiliate. In addition, the regulatory risk decision appears to be a unilateral decision made by the U.S. affiliate without the knowledge or approval of a centralized Headquarters function.

SECTION DELETED

"During the inspection, I also noted that the firm has submitted several (over 30) 15-day alert reports late to FDA over the past two years, excluding the non-US sourced case with the incorrect received date. (Ref 15 p. 10)

"Approximately 1,330 15-day alert reports have been processed and submitted to FDA during that time period. Dr. Thapar provided two lists of late reports and the reasons for being late (Exhibits 33, 34). (Ref 15 p. 11)

"During my review of 15-day alert reports, I also noted reports that were submitted late that were not on the list. Examples include: (Ref 15 p. 11)

SECTION DELETED "Case 2008AL001710, Digoxin Tablets, received on 2/7/2008 and submitted to FDA on 3/31/2008 (Exhibit 36). (Ref 15 p. 11) SECTION DELETED

"Due to limitations of the firm's database, Oracle AERS the firm was unable to generate listings of late reports. According to Dr. Thapar, the firm tracks late reporting by performing a manual monthly reconciliation of reports submitted to FDA; however, their manual system for tracking late reporting does not capture all reports submitted beyond the 15-day alert. For example, if the firm was conducting a monthly reconciliation of reports submitted to FDA for the month of March 2008, they would target only reports with a date received by manufacturer of March 2008 on the MedWatch I form. If a report was sent to the firm late (in March) from a foreign affiliate with a received date of 2/1/2008, this report would not be picked up as a late report during the reconciliation. In discussions with Dr. Thapar and Mr. Delicato regarding this

issue. Dr. Thapar stated they will look into purchasing a software program for the AERS database, if available, to allow them to conduct searches and manage late reporting.” (Ref 15 p. 11)

COMMENT: This FDA observation of persistent noncompliance with 15-day alert expedited reporting makes this a chronic problem, with FDA-483 observations from February 2006 reporting observations as early as 1999. The observation here of a faulty paper system for tracking compliance with expedited reporting timelines is indicative of an inadequate remediation for the inspection findings from February 2006 and is consistent persistent systemic problems with the Actavis pharmacovigilance system. Thus, the pharmacovigilance system is unlikely to support robust and reliable safety signal detection. In addition, the faulty tracking system for expedited reporting is consistent with the “total failure” of the Actavis Quality system also noted by the FDA inspectors in 2008. These widespread systemic issues with the Actavis quality system and pharmacovigilance system may contribute to inadequate signal detection for Digitek® (digoxin) Tablet cases.

“OBSERVATION 3 (Ref 15 p. 11)

SECTION DELETED

“Discussion with Management: (Ref 15 p. 12)

“Dr. Thapar provided periodic reports that were submitted to FDA beyond the established timeframe. For the past two years, there were two quarterly reports submitted late due to the firm's Regulatory Affairs department did not notify the Medical Affairs department of approval of the two products. XXXXXXXXXXXX Digoxin tablets XXXXXXXXXXXX did not observe any deficiencies or additional reports submitted late to FDA.” (Ref 15 p. 12) SECTION DELETED

COMMENT: Insufficient information for evaluation because of redaction of information.

“GENERAL DISCUSSION WITH MANAGEMENT(Ref 15 p. 13)

“I discussed the following item with the firm's Management during the inspection: (Ref 15 p. 13)

“Not all employees received training, in postmarketing adverse drug experiences. In discussion with Dr. Thapar and Mr. Delicate concerning training, they informed me that employees within Quality Assurance, Medical: Affairs, Legal, Customer Service and the receptionists receive postmarketing adverse. drug experience training; however, departments such as manufacturing and Regulatory Affairs do not receive the training. I stated that all employees should receive some level of training for adverse drug experiences in case they ever receive information that may meet the criteria for an adverse drug experience concerning any of the company's drug products. Dr. Thapar and Mr. Delicate stated that they understood my concern and indicated that they were going to add the ADE training for all employees.” (Ref 15 p. 13)

COMMENT: This is significant, in that no assurance is provided that employees will be able to correctly identify a potential adverse event, distinguish an adverse event from a product complaint or know to report the potential adverse events to the responsible person in the Drug Safety department.

“VOLUNTARY CORRECTIONS (Ref 15 p. 13)

SECTION DELETED

“Regarding the PADE inspection at the Actavis Totowa LLC, Little Falls, New Jersey location, deficiencies noted during the inspection included the following: (Ref 15 p. 13)

Expert Statement: Pharmacovigilance Systems in Digitek® (digoxin) Recall Page 54

- "Potential 15-day alert cases were not submitted to FDA.
- "Serious and unexpected reports were not promptly or adequately investigated. (Ref 15 p. 13)
- "Cases were not reviewed for seriousness and expectedness; submitted cases were classified as a 15-day alert report. (Ref 15 p. 13)
- "Periodic safety reports have never been submitted to FDA.
- "Written procedures have not been established (for follow-up investigations, adequate completion of MedWatch forms, maintenance of records to assure timely submission of 15-day alert reports and evaluation of adverse event data for serious outcome and event expectedness).

"In 8/2006, FDA sent a Warning letter to the firm as a result of the PADE inspection. The firm's corrective actions to the Warning letter included transferring reporting responsibilities for products manufactured in Little Falls, New Jersey to Actavis Elizabeth since the firm had established procedures and personnel. According to Sarita Thapar, Pharm. D., Director, US Medical Affairs, the products were merged into their operations and did not require additional procedures in review of the issues cited in the Warning Letter. I observed a similar deficiency during the current inspection. This deficiency concerned serious and unlabeled cases meeting the criteria for a 15-day alert report were not submitted to FDA (refer to FDA-483 Observation 1)." (Ref 15 p. 13)

COMMENT: This FDA observation of persistent noncompliance with 15-day alert expedited reporting makes this a chronic problem, with FDA-483 observations from February 8, 2006 reporting observations as early as 1999. An FDA Revised Warning Letter dated August 15, 2006 was written in response to the Amide response from February 28, 2006 to the FDA-483 issued on February 8, 2006. The Revised Warning letter reiterates the serious observations of noncompliance with expedited (15-day alert) reporting of serious, unexpected adverse events, and, in particular, they highlight the cases of Digitek® (digoxin) Tablets that were none submitted. The Warning Letter reiterates the serious findings regarding quality and completeness of the information on the 3500A MedWatch forms and the inadequate follow-up on serious cases. In addition, the FDA Warning Letter states "The specific violations noted in this letter are serious and may be symptomatic of underlying problems. You are responsible for investigating and determining the causes of the violations identified above and preventing recurrence of similar violations. (Ref. 4 p.3) Thus, the FDA inspection observation from May 20, 2008 that there were still unreported cases from January and February 2006 indicates that the pharmacovigilance system and accompanying quality systems remained inadequate to ensure compliance with regulatory reporting or the requirements of the compliance remediation. There was effective quality system with metrics to ensure the effectiveness of the corrective action. Paper tracking system for 15-day alert reports was inadequate. Late 15-day alert reports continued, some undetected (refer to Observation 2, above).

July 11, 2008 FDA response to Actavis response dated June 06, 2008 regarding FDA-483 observation. No further information was provided on this communication.

August 15, 2008 Actavis response to FDA response July 11, 2008 regarding FDA-483 observations issued to Actavis Elizabeth LLC on 12 May 2008.

- "Original OBSERVATION 1 (Ref 16 p. 2)
- "Adverse drug experience information has not been reported to FDA.

"Specifically, prior to 3/2006, non-U.S. sourced adverse drug experiences cases received by the firm's Denmark site were not forwarded to the firm's Elizabeth, NJ site for evaluation and submission to FDA. For example, approximately 40 serious and unlabeled cases, including 12 deaths that were received in January and February 2006, were not submitted to FDA. Examples include: (Ref 16 p. 2)

- a. *"Case GB-ACTAVISPR-20060193, received 1/17/2006 concerning a male patient who died following treatment with Verapamil"*
- b. *"Case GB-ACTAVISPR-20060216, reviewed 1/17/2006 concerning a male patient who died while being treated with diclofenac."*
- c. *"Case GB-ACTAVISPR-20060353, received 1/27/2006 concerning a female patient who died while being treated with metformin."*
- d. *"Case GB-ACTAVISPR-20060343, received 1/27/2006 concerning a male patient who died after starting treatment with metformin."*
- e. *"Case GB-ACTAVISPR-20060452, received 2/6/2006 concerning a female patient who died while being treated with diclofenac."* (Ref 16 p. 2)

"Follow-up comment/question:

"We understand that the retrospective analysis for non-US sourced adverse event reports will cover the period of December 19, 2005 through March 1, 2006. We remind you, however, that as of the acquisition date of December 19, 2005, your firm became responsible for all Alpharma products. As such, can you confirm that due diligence has been performed by your firm to assure that non-US sourced reports prior to December 19, 2005 were submitted in accordance with the regulations? (Ref 16 p. 2)

"Response:

"The submission of cases from December 19, 2010 through March 1, 2006, has not yet been reported because at the time of Actavis acquisition, the Global Pharmacovigilance group to Alpharma (located in Denmark) did not have an active exchange program for non-U.S. sourced adverse Drug events with the U.S. Medical Affairs Department. This fact was the subject of an MHRA inspection observation issued to Alpharma on October 20, 2005 prior to the referenced acquisition. The response to this MHRA inspection observation included a commitment to begin the exchange of non-U.S. sourced Adverse Drug Events with the U.S. as of March 1, 2006. Actavis LLC inherited this commitment with the acquisition and the exchange of non-U.S. sourced ADE's began as of 3/1/02 as required per this commitment. (Ref 16 p. 2)

"Actavis can confirm that it performed a due diligence review prior to the acquisition of Alpharma. As part of that due diligence, Actavis reviewed the results of the MHRA inspection and corresponding Alpharma response. The MHRA did not indicate the need for additional vigilance commitments with ADE reporting prior to march 1, 2006 commitment date. Actavis agreed to fulfill the commitments made to the MHRA inspection and initiated an exchange program as of March 1, 2006 which was the committed date. (Ref 16 p. 2)

"Attached is a copy of the MHRA cover letter, the specific observation, and the corresponding response to the MHRA observation for the exchange of foreign cases (see Section C.4.1.) (Ref 16 p. 2)

"Actavis, as stated in or original response dated June 6, 2008, reaffirms its commitment to report the non-U.S. sourced Adverse Drug events from the date of acquisition (December 19, 2005) through March 1, 2006." (Ref 16 p. 3)

COMMENT: These FDA inspection observations from May 20, 2008 indicates that the Actavis pharmacovigilance system and accompanying quality systems remained inadequate to ensure compliance with regulatory reporting or the requirements of the compliance remediation from either the MHRA inspection of 2005 or the FDA inspection from the first quarter of 2006.

“OBSERVATION 2: (Ref 16 p. 3)

“Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information. (Ref 16 p. 3)

- a. “Specifically, between July 2006 and August 2006, the firm’s Denmark site forwarded approximately 200 serious and unlabelled adverse drug event cases late to the firm’s Elizabeth, New Jersey site for processing and submission to FDA. Although the adverse drug experience information was collected by the Denmark site, the date received as reported on the MedWatch form was the date received by the Elizabeth, New Jersey facility. Examples include: (Ref 16 p. 3)
 - i. “Case 2006AL002139, Citalopram Hydrobromide Tablets, received by the firm’s Denmark site on 6/26/2006, date reported on the MedWatch for was 8/4/2006 and date submitted to FDA was 8/18/2006.
 - ii. “Case 2006AL002037, Naproxen, received by the firm’s Denmark site on 5/29/2006, date reported on the MedWatch for was 7/31/2006 and date submitted to FDA was 8/15/2006.
 - iii. “Case 2006AL001965, Citalopram Hydrobromide Tablets, received by the firm’s Denmark site on 4/4/2006, date reported on the MedWatch for was 7/24/2006 and date submitted to FDA was 8/8/2006.
 - iv. “Case 2006AL001977, Fluoxetine Oral Solution, received by the firm’s Denmark site on 4/28/2006, date reported on the MedWatch for was 7/24/2006 and date submitted to FDA was 8/8/2006.
 - v. “Case 2006AL001965, Citalopram Hydrobromide Tablets, received by the firm’s Denmark site on 3/10/2006, date reported on the MedWatch for was 7/24/2006 and date submitted to FDA was 8/8/2006.” (Ref 6 p.3)
- b. “Additionally, at least thirty (30) 15-day alert reports were submitted late to FDA between 4/2006 and 4/2008. Examples include: (Ref 16 p. 3)
 - i. “Case 2007AL004306, Diazepam Tablets, received on 2/26/2007 and submitted to FDA on 10/24/2007.
 - ii. “Case 2008AL001710, Digoxin Tablets, received on 2/7/2008 and submitted to FDA on 3/31/2008.
 - iii. “Case 2008AL001222, Amlodipine Besylate, received on 1/11/2008 and submitted to FDA on 3/7/2008.
 - iv. “Case 2008AL001104, Temazepam Capsules, received on 1/17/2008 and submitted to FDA on 3/7/2008.
 - v. “Case 2008AL00910, Tramadol Hydrochloride Tablets, received on 1/17/2008 and submitted to FDA on 3/7/2008.
 - vi. “Case 2008AL000910, Tramadol Hydrochloride Tablets, received on 1/7/2008 and submitted to FDA on 2/21/2008.” (Ref 16 p. 3)

"Follow-up comment/question: (Ref 16 p. 3)

"We acknowledge that your procedure MA-002-05, which defined Day 0 for 15-day alert reports, was corrected and revised on October 6, 2006. Additionally, we acknowledged your current corrective action which requires an investigation for any late submissions by foreign sources. You have committed to review cases submitted between March 1 and October 6, 2006 and submit corrected reports where necessary. Please explain why your review will not also include the period of December 19, 2005 through March 1, 2006. Additionally, as stated above, can you confirm that you have performed due diligence to assure that 15-day alert reports prior to December 19, 2005 were submitted with the correct dates? (Ref 16 p. 3)

"Response

"As stated in the response noted above (for observation/response #1), Actavis has committed to submitting non-U.S. Sourced adverse Drug events from December 19, 2005 through March 1, 2006 consistent with the commitment made as a result of the referenced MHRA inspection. When these cases are submitted to FDA, the initial Actavis receipt date (for our global affiliates) will be reported as Day 0 as opposed to the date the Adverse Drug event was received by our U.S. Medical Affairs department. This will ensure that all non-U.S. sourced Adverse Drug events are reported with an accurate receipt date back to the date of acquisition. (Ref 16 p. 3)

"In accordance with our previous response dated June 6, 2008, Actavis is committed to submitting all cases (as of 12/19/2005 0 with the correct date of receipt by 10/31/2008." (Ref 16 p. 3)

COMMENT: These FDA inspection observations from May 20, 2008 indicates that the Actavis pharmacovigilance system and accompanying quality systems remained inadequate to ensure compliance with regulatory reporting or the requirements of the compliance remediation from either the MHRA inspection of 2005 or the FDA inspection from the first quarter of 2006.

May 23, 2008 RECALLPACKAGE for DIGITEK® (digoxin) TABLETS

As part of the Digitek® Recall Package dated May 23, 2008, a Health Hazard Assessment was prepared by Dr. Jerrold Leiken at EVANSTON NORTHWESTERN HEALTHCARE OMEGA Corporate and Occupational Health Services. This is included in its entirety, and an extensive comment is added at the end.

"Health Hazard Evaluation - Digoxin Tabs 0.125 mg Reference Investigation log # 07-093(Ref 19 p. 2)

"Actavis Medical Affairs contracted Jerrold B. Leikin MD to perform a Health Hazard Evaluation (HHE) for the subject drug product. Specifically, to evaluate the impact of Digoxin Tabs 0.125 mg that were had a thickness approximately double to that required; this issue was found during packaging/filling operations on packaging line # 405 in November, 2007 (batch # 70924A1). (Ref 19 p. 2)

"Therapeutic use: Cardiac inotropic and anti-arrhythmic agent indicated for the treatment of mild to moderate heart failure. (Ref 19 p. 2)

"Root cause evaluation noted that the tablets found with double thickness might have been produced during the readjustment at start up. It was believed possible that the tablets might have been stuck in the tablet de-duster or metal detector and was not noticed by the press operator. (Ref 19 p. 2)

"Clinical conclusion: Potential risks to the patient depend upon the constituency of the tablets. If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. (Ref 19 p. 2)

"If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy. (Ref 19 p. 2)

"Based upon US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events for the time period of January 1, 2005 until March 31, 2008, a pattern of events were not identified for this product related or unrelated to known adverse events. Serious adverse events implies that such events are associated with death, a life-threatening event, caused permanent disability or damage, led to hospitalization, involved a congenital abnormality, or may have caused an important medical event. In this review, eleven adverse events were noted. (Ref 19 p. 2)

"Reported adverse event cases do not imply a direct cause-effect relationship of the product and the event since these are spontaneously reported cases that may have multiple confounding factors reported by known and unknown qualified sources. (Ref 19 p. 2-3)

- "26-MAY-2006 CASE 2006AL001331 PERIODIC Vision blurred. Lot # unknown.
- "05-JUL-2006 CASE 2006AL001672 PERIODIC Rash, Pruritis. Lot # unknown.
- "03-AUG-2006 CASE 2006AL002107 PERIODIC Diarrhoea, Fluid retention. Lot # unknown.
- "11-SEP-2006 CASE 2006AL002747 PERIODIC Blood pressure increased. Lot # unknown.
- "29-SEP-2006 CASE 2006AL002987 EXPEDITED Cardiac failure acute, cardiac failure congestive. Lot # unknown.
- "16-OCT-2006 CASE 2006AL003173 EXPEDITED Tremor, gait unknown abnormal, paraesthesia. Lot # unknown.
- "05-MAR-2007 CASE 2007AL000909 PERIODIC Drug ineffective, dysguesia, atrial fibrillation. Lot # 60400A1
- "10-MAY-2007 CASE 2007AL001896 PERIODIC Hyperaesthesia, burning sensation, erythema, cough, hoarseness. Lot # unknown.
- "01-JUN-2007 CASE 2007AL002191 PERIODIC Asthenia, Fatigue, Visual disturbance. Lot # unknown.
- "10-JAN-2008 CASE 2008AL000238 PERIODIC Medication error. Lot # unknown.
- "20-MAR-2008 CASE 2008AL001820 PERIODIC Heart rate increased, Drug ineffective. Lot # unknown.

"Jerrold B. Leikin MD, Director of Medical Toxicology ENH OMEGA" (Ref 19 p. 3)

COMMENT: Review of the health hazard assessment (HHE) revealed a "Clinical conclusion: Potential risks to the patient depend upon the constituency of the tablets. If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If the increased thickness is due to clinically inert substances, then a decreased amount of

digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy. The reviewer concurs with this assessment.

However, here were missing details in the analysis contained in the HHE. A table/list of events is included, but it is not discussed if this is a comprehensive sample or a representative subset. Eleven (11) spontaneous reports are included in a Table. However, they are not reviewed in detail for toxicity or decreased efficacy. In addition, reference is made to an "US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events for the time period of January 1, 2005 until March 31, 2008" for Digitek® (digoxin) Tablets that appears to be an Analysis of Similar Events with Signal Detection for eleven (11) cases. However, details of this review or critical evaluation of this review is not included. No analysis of accompanying complaint data, analytical data or complaint investigations is provided. The US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events for the time period of January 1, 2005 until March 31, 2008 was not provided as a part of this review to allow independent evaluation of the data.

COMMENT: Thus, it is my opinion based on reasonable evidence that there were alterations in the press release to the healthcare providers and the general public that may have decreased the magnitude of the risk communicated to healthcare providers and patients. This occurred in the communication of two separate issues: (1) one on the definition of the patient groups at increased risk and (2) a second on two potential adverse outcomes for the double-thick digoxin tablet. These issues are discussed in sequence, below and on the following pages:

Definition of High-Risk Patient Groups: (1a) Patients with daily dosing and (1b) 1b. Patients with renal insufficiency versus patients with renal failure:

The Health Hazard Assessment by Dr. Jerrold Leikin dated 18-Apr-2008 (Ref 18) delineated two subgroups of patients that were at risk of digoxin toxicity if they received double-thick tablets with twice their normal daily dose: "If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency." The letter in the recall package to the business-to-business customers (Ref 17), reiterated Dr. Leikin's warning on the two high risk groups: "Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency."

Regarding communication with healthcare providers and the general public, there were no "Dear Prescriber" or "Dear Patient" letters provided in the Recall Package dated 23-May-2008 or in the dossier provided me for review. Thus, one can assume that the communication to the healthcare community and general public appears to have occurred only through the press release in the Recall Package from 23-May-2008 (Ref 17). The Recall Package included a press release that contained a different statement on the patient groups at high risk for digoxin toxicity: "The existence of double strength tablets poses a risk of digitalis toxicity in patients with renal failure." Thus, in the press release to the general public, there was omission of the high risk group of "individuals on daily dosing" and alteration of the high risk group of "patients with renal insufficiency" to include only "patients with renal failure."

"Renal insufficiency" defines a patient subgroup with insufficient excretion of wastes by the kidneys. "The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased kidney glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for 3 or more months. Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR. The different stages of chronic kidney disease form a continuum in time; prior to February 2002, no uniform classification of the stages of chronic kidney disease existed. At that time, K/DOQI published a classification of the stages of chronic kidney disease (Ref 25), as follows:

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m²)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m²)
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m²)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m²)
- Stage 5: Kidney failure (GFR <15 mL/min/1.73 m² or dialysis)

Specifically, the term "renal failure" is applied only to patients with the Stage 5 chronic renal failure with GFR <15 mL/min/1.73 m² or dialysis). Clinically, "renal failure" may be subdivided into either "acute renal failure" or "chronic renal failure," but both subgroups define a more severe degree of renal impairment. Thus, substitution of the term "renal failure" for the term "renal insufficiency" in the press release decreases the size of the at risk group and fails to include patients with lesser degrees of renal impairment that may also be at risk of digoxin toxicity with the double-strength, double-thick digoxin tablets.

(2) Alternative Adverse Clinical Outcomes: (2a) Risk of Overdose (digoxin toxicity, include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia) versus (2b) Risk of Underdose (exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy):

The Health Hazard Assessment by Dr. Jerold Leiken dated 18-Apr-2008 (Refs 17, 18) described two potential and disparate risks that could be associated with ingestion of the double-thick tablets with twice their normal daily dose:

"Clinical conclusion: Potential risks to the patient depend upon the constituency of the tablets. If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake.

"If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy." (Ref 17, 18)

The letter in the recall package to the business-to-business customers (Ref 17), reiterated Dr. Leiken's warning on the two potential risks with the double-thick tablet:

"Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy."

Regarding communication with healthcare providers and the general public, there were no "Dear Prescriber" or "Dear Patient" letters provided in the Recall Package dated 23-May-2008 or in the dossier provided me for review. Thus, one can assume that the communication to the healthcare community and general public appears to have occurred only through the press release in the Recall Package from 23-May-2008 (Ref 17). The Recall Package included a press release that contained a statement on the alternative risks of the double-thick digoxin tablet that was substantially different from the statement made by Dr. Leiken in the health hazard assessment:

"Digitalis toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can also result from excessive Digitalis intake. Several reports of illnesses and injuries have been received."

Specifically, the statement "If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease

(congestive heart failure and arrhythmia) due to lack of therapeutic efficacy” has been omitted from the press release to the general public. Thus, omission of the second potential adverse outcome in the press release decreases the size of the patient group at risk group and fails to include patients at risk for exacerbation of underlying congestive heart failure or underlying cardiac arrhythmias secondary to lack of efficacy of subtherapeutic doses of digoxin.

In summary, there were three alterations of the risk communication in the press release to the healthcare providers and the general public as compared to the Health Hazard assessment and the “Dear customer letter” for the business-to-business customers:

- (1) The omission of patients on daily dosing as a group at increased risk for digoxin toxicity with a supratherapeutic double-thick digoxin tablet.
- (2) Change of the terminology from “renal insufficiency” to “renal failure” to define the group at increased risk for digoxin toxicity with a supratherapeutic double-thick digoxin tablet.
- (3) Omission of the alternative clinical scenario of lack of efficacy and exacerbation of underlying congestive heart failure and/or cardiac arrhythmia with subtherapeutic double-thick digoxin tablets.

It is my opinion that this to the general public and the healthcare community does not adequately communicate the full extent of the health risk, because it alters patient population at risk of digoxin toxicity by (1) omitting the patient population on daily dosing and altering the patient population with impaired renal function to include only those with the advanced stage of renal failure and omit those with lesser disease severity of renal insufficiency. Both of these patient populations were defined as at increased risk in the health hazard assessment by Dr. Leiken dated April 18, 2008. Thus, it is my opinion that this press release to the general public and the healthcare community does not adequately communicate the full extent of the health risk to the entire patient population at risk for lack of efficacy because subtherapeutic dosing.

Inspection 7 Little Falls, NJ 10Jul08-10Aug08

From 10Jul08 – 10Aug08, the FDA conducted an inspection on the Little Falls, NJ site. On June 23, 2008 an FDA-483 inspection observations relevant to the assessment of the impact on the Digitek® case.

June 23, 2008 release date Establishment Inspection Report from inspection 10Jul08 -10Aug08

SUMMARY (Ref 20 p. 1)

This inspection of a pharmaceutical manufacturer was conducted as part of the NWJ -DO FY06 Drug Work-Plan under FACTS Assignment # 3474850, Operation 1D # 2780701. Provided as Pre-approval Inspectional guidance was afforded through Compliance Program Guidance Manuals. 7365.002: Drug Manufacturing Inspection and 7346.8-2: Pre-Approval Inspections/Investigations. The previous inspection of 1/10/2006 et. al., provided follow-up GMP Coverage and Surveillance coverage of the Postmarketing Adverse Drug Experience Reporting System as requested by the Center for Drug Evaluation and Research, Surveillance Program Team Division of Compliance Risk Management and Surveillance, Office of Compliance. Significant deficiencies were observed regarding the PADE reporting system. Deficiencies were also observed regarding the GMP Quality System. Firm management promised corrections and a written response within 10 days to the New Jersey District. The inspection was classified OAI for PADE reporting and VAI for GMPs. (Ref 20 p. 1-2)

The Quality, Production, Laboratory Control and Materials Systems were covered during the current inspection. Limited coverage was also provided to the Facilities & Equipment System as necessary, but this system was not covered in its entirety. An FDA-483, Inspectional Observations, was issued at the closeout meeting regarding deficiencies in the areas of Quality Control, laboratory records,

OOS and production investigations, cleaning validation, bulk stability testing, detection and documentation of OOS results, sampling documentation: equipment qualification, calibrations and preventive maintenance, rejected materials and storage of components. In addition, a discussion was held with management regarding the labeling of laboratory glassware and stability of solutions. Corrections were promised for all observations and discussion items. Corrections to the previous PADE inspection will be verified under a separate assignment." (Ref 20 p. 1-2)

COMMENT: A copy of the Establishment Inspection Report from the additional inspection mentioned above will permit verification of the corrections of the previous PADE inspection and would add to the complete analysis of the case.

August 14, 2008 e-mail from PAREXEL consultant Michael Falkow regarding review of Digitek® adverse events and quality systems issues

"Misbah:

"Some of my thoughts from my review of the AE's for digoxin follows. (Ref 21. p. 1)

"These Medical Affairs observations are in mind as to what may a litigation attorney charge after a discovery review of these same documents:

"Medical Affairs-

1. "Lack of diligence in contacting reporter so as to obtain requisite information. (Ref 21. p. 1)
- "There are instances where the "Actavis Medical Affairs Case Form" indicates once, "LMNM" (left message/voicemail, with no additional attempts documented and no further information. (Ref 21. p. 1)
- "Two (2) calls attempted on the same day; meets SOP requirement but . . (Ref 21. p. 1)
- "Instances where person contacted states, "not a good time to talk" and no subsequent follow-up. (Ref 21. p. 1)
- "One contact, "would only talk to Patrick" with no indication of any additional information or follow-up. Instances where initial contact reported "number unavailable" or "number disconnected." However, there was one instance in which a number was attempted to be determined by searching the internet. This raises the question, "Why was this not done each similar time?" (Ref 21. p. 1)

"Quality Systems Issues-

"2. Routinely, areas on the "Actavis Medical Affairs Case Form" are not completed. There is no indication as to whether an attempt was made to get the information but was refused, or if it is n/a, etc. By leaving areas blank with no notation, I do not know if the question was asked or omitted. (Ref 21. p. 1)

"3. There is no system to marry a returned bottle to a complaint 1 AE so that the lot number can be determined. When reported that the bottle was returned, there routinely is no indication to whom the reported returned the bottle- pharmacy, Actavis, 3rd party. (Ref 21. p. 1)

"4. What is the date of complaint? "Date of Complaint" recorded on the Product Complaint Form F-SOP-0034.01 is typically dated 1 1/2 months after the date received as recorded on the Actavis Medical Affairs Case Form." (Ref 21. p. 1)

COMMENT: Observations by consultant Michael Falkow are indicative of persistent problems with the pharmacovigilance system and the broader systems that link, product complaints, quality investigations, and health hazard assessments (safety signal detection) by drug safety.

The Revised Warning Letter dated August 15, 2006 was written in response to the Amide response from February 28, 2006 to the FDA-483 issued on February 8, 2006 reiterated the serious findings regarding quality and completeness of the information on the 3500A MedWatch forms and the inadequate follow-up on serious cases. The Amide response to the FDA-483 observations from February 8, 2006 did not provided sufficient information give assurance that the inspection findings would be followed by an aggressive compliance remediation program with root cause analyses, CAPA system, revised business processes, and a quality system with metrics to assess the effectiveness of the new systems. Repeat inspection from April to May 2008 revealed similar findings for expedited ADE reporting and inadequate compliance tracking systems was also indicative of persistent systemic issues that may have interfered with safety signal detection. Mr. Falkow's observations are yet further evidence of a widespread quality failure in pharmacovigilance and complaint handling that may have lead to inadequate safety signal detection in regards to the risk of digoxin toxicity or lack of efficacy from the double thick Digitek® (digoxin) tablets.

October 16, 2008 Action Plan for closing all Digoxin related complaints.

Actavis developed an Action Plan for closing all digoxin-related product complaints that were reported in the aftermath of the Digitek® (digoxin) Tablet recall. At the time that the plan was approved, there was a back log of approximately 3000 open complaints related to Digitek® (digoxin) Tablets.

SUMMARY

"The subject action plan is being set forth to establish an action plan to close all complaints related to Digoxin Tablets. As of today, there are approximately 3,000 open complaints solely related to Digoxin Tablets. All complaints closed to date have been done so properly and compliantly, however, to ensure that a proactive approach is being implemented to address the situation at hand, QAIG Management has decided to implement the following action plan. (Ref 22. p. 7)

"During the first week of May 2008, the Quality Assurance Department began receiving an abundance of complaints as the result of the Class I recall for Digoxin Tablets, 0.125 mcg and 0.250 mcg. Due to the enormous volume of complaints received in a short time period, the processing and evaluation of the complaints could not be immediately performed. Furthermore, as the majority of these complaints are Adverse Drug Events, additional information from the Medical Affairs Group is required prior to closure; which has also affected the closure of complaints within the 30-day requirement specified in SOP # 0034 (Handling of Product Complaints) and further escalated the number of complaints on hand. See the enclosed graph, which represents the volume of complaints received by month prior to the Digoxin Tablet Recall (January 2008 - April 2008) and the volume of complaints received after the Digoxin Tablet Recall (May 2008 - September 2008). (Ref 22. p. 7)

"The following is a step-by-step action plan to proactively address the current situation regarding complaints, which has been assessed by QA Management. (Ref 22. p. 7)

"Action Plan:

"1. Obtain at least two individuals, internally or externally, to aid in the processing and entering of complaints into the Access Database to fully and accurately assess the number of complaints open and/or backlogged. (Ref 22. p. 7)

"2. At a minimum, each individual within the Complaint Group will process 30 complaints per business day. (Ref 22. p. 7)

"3. One individual within the Complaint Group will monitor the shared drive that Medical Affairs puts newly initiated complaints and/or additional information for open complaints into on a daily basis to ensure that those complaints are immediately processed so that they do not exceed the 30 day closure time-frame as required by SOP # 0034. (Ref 22. p. 8).....

"Furthermore, to ensure efficiency, the Medical Affairs Department will be required to send the Complaint Group a detailed daily notification of all complaints received on a given day and any additional information received related to any open and/or closed complaints. (Ref 22. p. 8)

"4. One individual within the Complaint Group will monitor the Access Database daily to ensure that if a complaint is expected to exceed the required time-frame, an Interim Retort will be prepared and submitted for approval prior to the complaint reaching the 30 day. (Ref 22. p. 8)

"5. SOP # 0034 is being revised to make the complaint handling process more efficient. In doing so redundant steps are being eliminated, which will reduce the complaint processing time. (Ref 22. p. 8)

"6. All Digoxin backlogged complaints are expected to be closed within the next 6 months. (Ref 22. p. 8)

"7. All other backlogged complaints are expected to be closed within the next 2 months. (Ref 22. p. 8)

"8. All future complaints that are received, with the exception of Digoxin related complaints, will be closed within the required 30 calendar days from the date of receipt. (Ref 22. p. 8)

"9. In the event that Actavis receives an enormous volume of Digoxin related complaints in the future, the complaints will be closed within a 3-month time period." (Ref 22. p. 8)"

COMMENT: This action plan was developed on October 16, 2008 to address issues arising from the Digitek® (digoxin) Tablet Recall dated May 23, 2008. It is my opinion based on reasonable evidence, that this plan is reactive, not proactive.

COMMENT: The plan provides a process for the completion of the product complaints, but it does not address an associated quality system to ensure that the product complaints are closed out with adequate completeness and quality. In addition, there is no assessment of the resources needed to complete the closeout of the product complaints in a timely manner. No information is provided on metrics to give assurance of the effectiveness of the system. It is my opinion based on reasonable evidence, that this plan is further evidence of the inadequate complaint handling processes, inadequate personnel staffing, and inadequate quality systems that were the underlying cause of the problem that lead to the recall of Digitek® (digoxin) Tablets.

Excerpts from Institute for Safe Medication practices QuarterWatch 2008 Quarter 2

"Reports of serious injury, disability, and death associated with drug therapy exceeded 20,000 cases for a second consecutive quarter in 2008. For the first half of 2008, the number of serious adverse drug events reported to the Food and Drug Administration was 40% higher than the average for the four quarters of 2007."

"In the second quarter, two drugs contributed substantially to the increase for the first time. A massive recall of the heart drug digoxin – affecting 60% of the nations supply – helped spur reports of 650 patient deaths – but a direct link to the defective tablets was difficult to assess.

"The ISMP Quarter Watch pilot monitoring program evaluates computer excerpts of all serious, disabling and fatal adverse event drug events reported to the FDA for patients in the United States. The U.S. system for postmarketing safety surveillance relies on voluntary reports from consumers and health professionals, and the submission of such a report does not in itself prove that the suspect drug caused the event described. Is not known what percentage of all such events that occurred are voluntarily reported, although available data show only a small fraction of patient injuries associated with drug therapy are ever reported.

"The highlights of the second quarter of 2008 (April – June) are as follows:

"Trends over time:

"In the second quarter of 2008, the FDA received 22,980 reports of serious injury associated with drug therapy, including 2968 deaths and 585 cases of disability or birth defect. The total also included 1397 cases attributed to medication error.

"The 2968 reported patient deaths in the second quarter declined from a record of 4824 in the previous quarter, but remained substantially higher than in the previous year.

"Plotting time trends for serious injuries was complicated by a technical clarification by the FDA which permitted capturing 2109 additional serious injury cases that would not have been detected using previous QuarterWatch criteria. Without this technical change, serious injuries, disability and death combined were similar to the previous quarter – an increase of 126 cases.

"Signal for specific drugs

"Digoxin (DIGITEK® brand)

"The most striking signal was seen for the generic heart drug digoxin, which accounted for 1882 reports of serious injury, including 650 patients' deaths – more cases than accounted for any other prescription drug in the second quarter. Digoxin is used by the more than one million patients with heart failure – a medical condition in which the declining output of the heart is causing serious medical problems.

"We linked the majority of these reports – and others from earlier quarters – to as consumer level recall in April 2008 by the Actavis group, a large generic drug manufacturer based in Iceland. The company report 'the possibility' that it was distributed double strength tablets and recalled the entire unexpired production of it Little Falls, NJ, plant and the company's 3 New Jersey plants remained closed.

"When we first learned of the scale of reported injury and death in November, we immediately notified the FDA and through the ISMP newsletter and consumer website warned consumers and health professional to check the Establishment Inspection Report suppliers to ensure they did not have recalled tablets (1, 2). The ISMP consumer website (www.consumermedsafety.org) has partnered with igaurd.org to provide help in identifying the recalled tablets. While most cases of patient injury and deae3th could be linked to patients who reported having taken the recalled tablets, the evidence was less clear whether they had received tablets that were

overstrength or had other specific defects. This is because a small overdose of digoxin can be toxic to vulnerable heart patient even without an overstrength tablet, and the recall notices could have simply alerted thousands of patients to the well-established dangers of this drug.

"The existing evidence does not permit us to either rule out or state definitively, whether defective digoxin tablet led to hundreds of patient deaths. We analyze the data and examine the unanswered questions in a separate Dossier I: Section of this report.

"The Adverse Event Reporting System

"Reports from health professional increased in the first quarters of 2008 by 42% compared to the mean of the four quarters of 2007. Reports from consumers increased slightly more, by 46% in 2008 compared to the average for 2007. We estimate that approximately 2% of this increase occurred because of the technical adjustment for certain reports described below.

"The FDA clarified, at our request, an ambiguity in its guidance for analyzing adverse events that were directly reported to the agency, rather than through manufacturers. It previously had been reported to the agency, rather than through manufacturers. It previously had been impossible to separate reported events that were to our capturing an additional 2109 serious events in the second quarter that would have otherwise been excluded as "other than serious"

"Conclusions

"The results of the latest QuarterWatch expose two shortcomings in the system for protecting patient safety and minimizing the risks of valuable prescription drugs.

"The size and scope of the digoxin recall, together with six other major recalls in 2008, show that large quantities of important generic drugs are not being manufactured to adequate quality specifications. We recommend creating a task force to conduct an independent review of the FDA's systems for inspecting companies, notifying consumers about recalls, and assessing possible harm to patients.

"Furthermore, in both the digoxin and the Cases, modest public notices issued by the FDA triggered an outpouring of adverse events reports, once patients and doctors started to make the connection between the symptoms and the drug. This response suggests that extent to which patient injury associated with prescription drug therapy is being routinely underreported.

BIBLIOGRAPHY

- Ref 1. July 9, 2004 Amide Investigation report: Digitek® (digoxin) "double-thick" tablet
- Ref 2. February 8, 2006 FDA-483 Form Inspection Observations issued For Inspection 3 - Totowa, NJ 17Jan06 – 08Feb06.
- Ref 3. February 28, 2006 Amide Pharmaceuticals response to FDA-483 Form Inspection Observations issued February 8, 2006.
- Ref 4. August 15, 2006 Warning Letter based on company response dated February 28, 2006.
- Ref 5. September 06, 2006 Company response to August 15, 2006 Revised Warning Letter.
- Ref 6. August 10, 2006 FDA-483 Form Inspection Observations for FDA inspection of 10Jul06 – 10Aug06
- Ref 7. February 01, 2007 FDA Warning Letter for Inspection based on August 10, 2006 FDA-483 Form Inspection Observations issued for FDA inspection of 10Jul06 – 10Aug06
- Ref 8. June 28, 2008 release date Establishment inspection report based on FDA-483 Form Inspection Observations dated August 10, 2006 issued for FDA inspection of 10Jul06 – 10Aug06
- Ref 9. November 17, 2006 EIR for Inspection 18Sep06-11Oct06, Little Falls, NJ
- Ref 10. September 28, 2007 FDA-483 Form Inspection Observations issued for FDA inspection of 05Sep07 – 28Sep07 of the Little Falls, NJ site.
- Ref 11. May 7, 2008 release (Date unknown) Establishment Inspection report based on FDA-483 Form Inspection Observations dated September 28, 2007 for FDA inspection of 05Sep07-28Sep07.
- Ref 12. May 20, 2008 FDA Inspection Close Out of Inspection, 18Mar08 – 20May08, Totowa, NJ
- Ref 13. May 20, 2008 FDA-483 Form Inspection Observations based on inspection 18Mar08 – 20May08
- Ref 14. May 28, 2009 release (Date unknown) Establishment Inspection report based on FDA-483 Form Inspection Observations dated May 20, 2008
- Ref 15. May 21, 2008 FDA-483 Form Inspection Observations observation Inspection, 21Apr08-21May08 of the Elizabeth, NJ site.
- Ref 16. August 15, 2008 Actavis response to FDA response July 11, 2008 regarding FDA-483 Form Inspection Observations dated May 21, 2008 from FDA Inspection of 21Apr08-21May08 of the Elizabeth, NJ site.
- Ref 17. May 23, 2008 Digitek® (digoxin) Tablets RECALL PACKAGE dated 23May2008.
- Ref 18. Digitek® (digoxin) Tablets Health Hazard Assessment, Dr. Jerrold Leiken, April 18, 2008 included in Digitek® (digoxin) Tablets RECALL PACKAGE dated 23May2008.
- Ref 19. June 23, 2008 release date. Establishment Inspection Report from FDA Inspection of 10Jul08 - 10Aug08 of the Little Falls, NJ site.
- Ref 20. August 14, 2008 E-mail from Michael Falkow, PAREXEL consultant, to Misbah Sherwani, Senior Quality Assurance Investigations Manager, regarding review of Digitek® adverse events and quality systems issues. (August 14, 2008 2:07 PM). Bates ACTAV 000308945.
- Ref 21. October 16, 2008 Memo from Danielle Cowrie, Actavis employee, to Misbah Sherwani, Senior Quality Assurance Investigations Manager regarding Action Plan for closing all Digoxin related complaints. Bates ACTAV 000655812-000655813.

Ref 22. Institute for Safe Medication Practices QuarterWatch 2008 Quarter 2

Ref 23. National Kidney Foundation. *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification*. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1).

Technical Report and Analysis

Digitek Tablets

Russ Somma, Ph.D.

SommaTech, LLC

June 15, 2010

Executive Summary

Professional Experience

I have more than 35 years of experience working in the pharmaceutical industry, specifically in the areas of production troubleshooting, dosage form development, manufacturing scale-up, technology transfer and project management. My particular technical interest is in the area of solid dosage forms and the physical pharmacy associated with them. I was employed by Novartis for the majority of my career, and have held leadership positions with direct responsibility for senior staff, including international, as well as cross- and multi-functional teams. This has included providing technical development and life cycle management support for a variety of oral solid dosage, novel formulations and therapeutic groups. Additionally, I have served as an invited investigator trainer and liaison for the FDA on various projects and initiatives, affording a unique perspective within Pharmaceutical Regulatory Affairs.

I lead the industry that enabled the implementation of SUPAC IR/MR equipment guidance within FDA/CDER.

As a recognized industry subject matter expert in technology transfer and Quality by Design I have been a welcomed keynote speaker and presenter at many association meetings and conferences. Topics include "Current Industry Practices in Manufacturing Process Validation", "Technology Transfer or Knowledge Transfer for Products and Processes: Which Expedites the Process Most?" and "Life Cycle Management – the Way of the Future?"

In addition I have written and co-authored numerous articles, technical papers and studies in peer reviewed journal and publications such as *Pharmaceutical Engineering*, *Journal of Pharmaceutical Innovation* and, most recently, *Pharmaceutical Executive*.

Education

- Ph.D. – Pharmaceutical Science, Rutgers University
- M.S. – Pharmaceutical Science, Rutgers University
- B.S. – Pharmacy, Rutgers University

Awards

- Named to "Who's Who in Science & Engineering"
- Letter of commendation for efforts surrounding the SUPAC equipment list, sent by Susan M Setterberg, Mid-Atlantic Region, FDA, dated April 7, 1997.



- “Hammer Award” winner, presented by Vice President Gore’s Committee for National Performance Review, 1998
- “Special Recognition Award” presented by CDER Director, Janet Woodcock MD, for invaluable service and technical support to FDA in the development of the SUPAC-IR Equipment Guidance. “Ispeak 18 (1) 1-2 (1998)
- 2007 Recipient of ISPE’s prestigious Max Seales Yonker Member of the Year Award

Introduction

This report is the work product from our review of the technical aspects and the manufacturing process for the product Digitek. Digitek is the trade name for digoxin tablets manufactured by Actavis. The product is supplied in two strengths 0.125mg which is a yellow round tablet having a B and 145 on the scored side / plain on the reverse side of the tablet and 0.250mg which is a white round tablet having a B and 146 on the score side / plain on the reverse side of the tablet. The focus of our review centered on the manufacturing processes and technical aspects surrounding that product.

The reason for the review is a response to a request by the Motley-Rice law firm for our expert opinion concerning the events evolving from the manufacture and distribution of digoxin tablets under the trade name Digitek. These events include the final distribution of a batch within which a pharmacist who was dispensing the product in the field reported “double thick” tablets.

Actavis manufactured batch #70924A in November 2007. The technical review included the manufacturing batch record (MPR #14504) as well as related documentation, which included internal investigations, as well as all in-process records through packaging.

Some of our technical observations were subsequently used to confirm the characteristics of the process equipment used for digoxin manufacture by a walk through of the Actavis facility on June 3, 2010. This walk-through was conducted in conjunction with attorney’s Peter Miller and Meghan Johnson Cater. During this inspection all the equipment and related questions as related to the equipment were adequately addressed with no open issues.

Blending

Digitek is manufactured using a dry blend / direct compression process. The term dry blend means that the active pharmaceutical ingredient (API) is mixed directly with the required inert / excipient materials without the use of a solvent to form the final blend. The concept of a direct / dry blend is best visualized using the following generalized schematic which outlines typical process steps for pharmaceutical manufacture of oral solid dosage forms such as digoxin tablets.

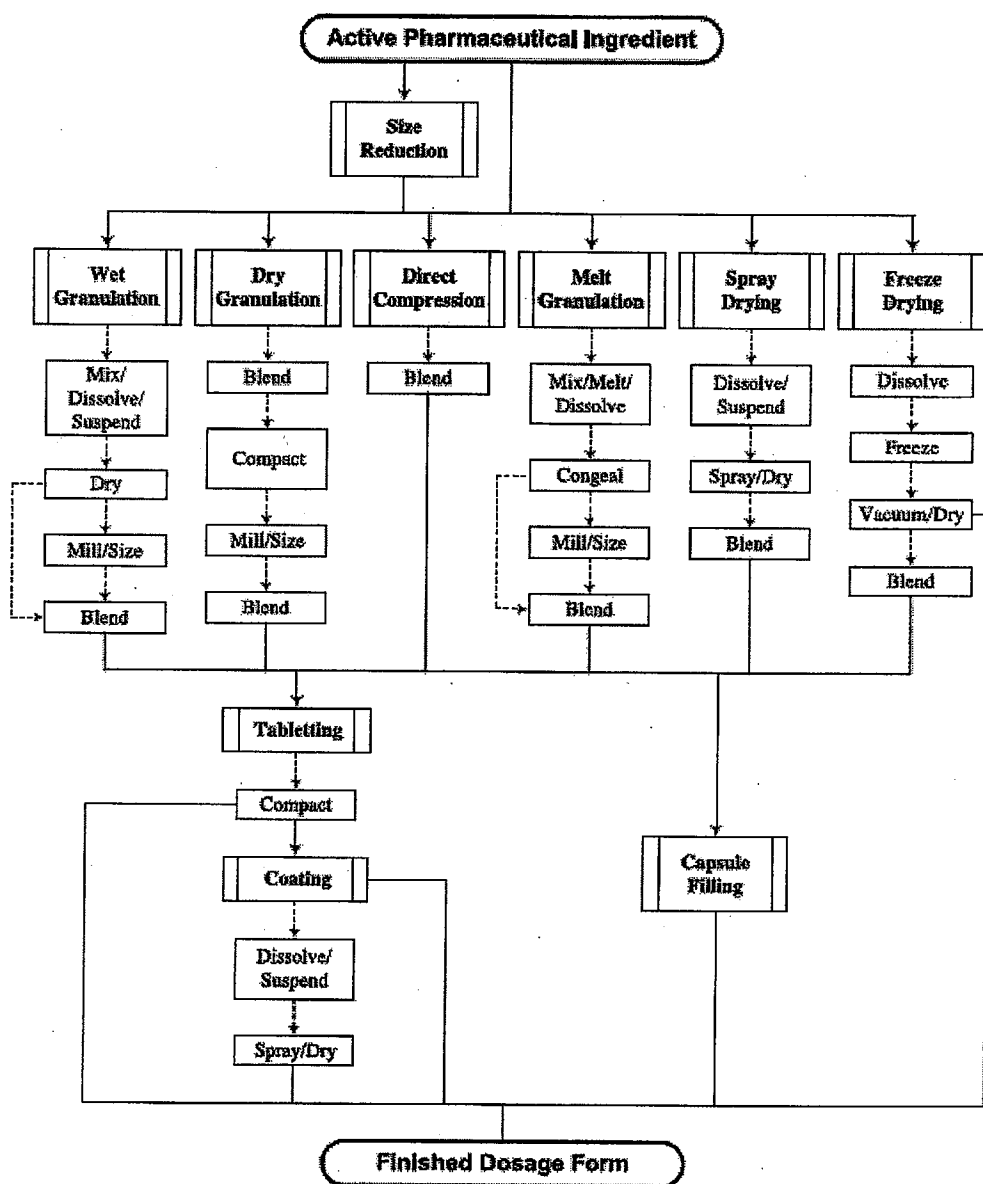


Fig. 4. Common processes for preparing solid oral dosage forms.

(Ref: Zhang et al, Advanced Drug Delivery Reviews, p.371-390, 2003)

The composition of the Digitek blend (504kg.) and the tablet / unit (105.0mg) are shown in the following chart which is taken from MPR#14504 which was used for batch #70924A.

BATCH SIZE: 4,800,000 TABLETS		EXP. DATE:	
THEO. WT.: 105.0 mg		AVG. WT. RANGE (10 TABS): 1.019 - 1.082 g	
ITEM ID NUMBER	RAW MATERIAL NAME	AMOUNT PER UNIT (mg)	QUANTITY REQUIRED (kg)
3115	Corn Starch, NF	7.525	36.12
0111	Digoxin Micronized, USP*	0.125	0.608 (N)
3044	D&C Yellow #10 Aluminum Lake, 15%-20%	0.10	0.480
3090	Croscarmellose Sodium, NF	4.00	19.20
3051	Lactose Hydrous Impalpable, NF*	17.85	85.672 (O)
3088	Starch Pregelatinized, NF	20.0	96.00
3059	Microcrystalline Cellulose, 101, NF	20.0	96.00
3050	Lactose Anhydrous D.T., NF	32.0	153.6
3089	Stearic Acid, NF	1.0	14.40
3081	Silicon Dioxide, NF	0.4	1.920
	TOTAL WEIGHT	105.0	504.0

* Calculate the quantity of Digoxin Micronized, USP (N) and Lactose Hydrous Impalpable, NF (O) based on moisture content of Digoxin Micronized, USP. Refer to Page # 2 and # 3 for calculations.

The amount of digoxin (API) to be used in the batch is corrected to account for the assay value of the API and assures that the desired amount of API is included in the blend. The blending process did not show any procedural issues or unexpected deviations from the established directions and planned deviations as set in place.

The final blend is tested as an in-process control and is required to meet the requirements of 90-110% with an RSD of less than 5.0% for digoxin content using an average of 10 samples taken through-out the blend. The samples are withdrawn from the blender using a sample thief. Three sets of samples are taken to assure material is available should a repeat blend test be required. Batch 70924A was found to meet these requirements without the need to conduct any testing using the replicate samples.

This finished and tested blend is then used to feed the compression equipment / tablet press to make the finished tablets. It should be noted that a change in the specifications was made such that the results are reflective of an "average" of the 10 thief / blend samples rather than on an "individual" of each of the 10 samples. This was properly documented and the regulatory notification as annual reportable had been addressed for the product.

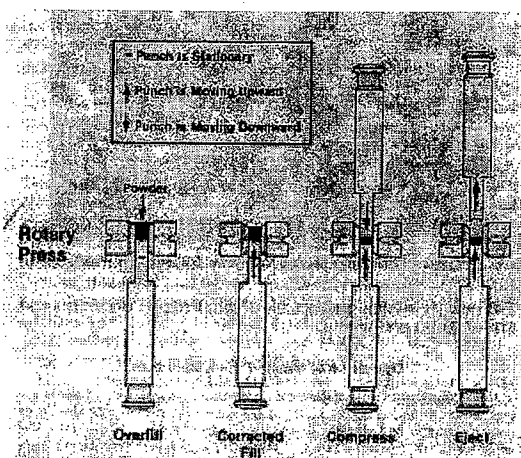
During our review it was clear that blend homogeneity problems had been seen during the testing of other batches. These problems varied in nature but were attributed to analytical testing errors and sample manipulation and recovery from the blending process. It is our experience that blend sampling and testing are difficult. This appears to hold in this case as the data reviewed would support the firm struggled with this task.

Compression / Tableting

The tableting operation was conducted using two tablet machines. These were tablet machines # 67 and #71. Both machines were manufactured by Stokes. The tooling used was flat-faced beveled edge with the debossing previously described for Digitek 0.125mg. The tablet operation is monitored by a tableting operator who checks machine functionality and confirms the tablets are within the in-process specifications for thickness (2.0 – 3.0 mm) hardness (1.0 – 6.0 kp) and weight (0.097 – 0.114 gm) for ten tablets. These tests are conducted on an hourly basis and recorded through out the compression run for the entire batch (4.8 million tablets).

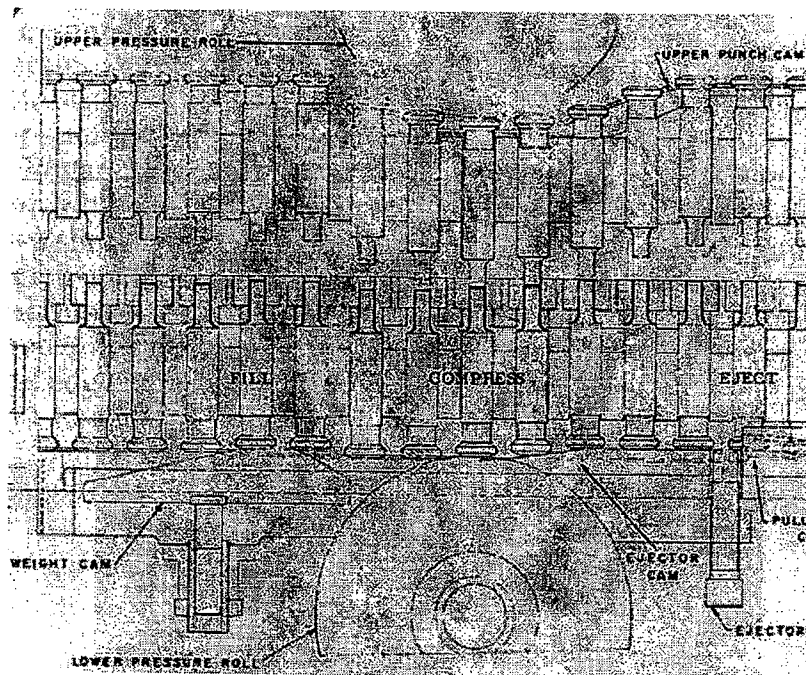
No remarkable events were seen during our review with the exception of an event recorded on page 2711. The records noted that the machine was stopped to clean the tablet tooling (upper and lower punches) since there was some "picking" being observed. The term picking is used to describe the adhesion of some of the tablet blend to the tablet tool tips / punch faces. This was seen on machine #67 and not on # 71. The cleaning was completed and the machine was re-started after confirmation of the tablet specifications were being maintained.

To relate the terms used in tablet formation the following schematic is provided which shows a single station of tablet tooling. This comprises an upper and lower punch as well as a die. It becomes obvious upon inspection of the schematic that the lower punch and the die form a void into which the blend flows. The lower punch moves up after adjustment to achieve the correct fill level. The upper punch then enters the die and applies force to the blend by reducing the available volume between the upper and the lower punch within the confines of the die. Once the punch reaches its maximum distance of penetration it withdraws from the die and the lower punch moves up and ejects the finished tablet out of the die.



(Ref: Remington: The Science and Practice of Pharmacy, 19th Edition, 1995, Mack Publishing, Easton, PA)

The following schematic is provided to better visualize punch movement in the machine as well as to give context to the aspects leading to tablet formation using a tablet machine with multiple stations of tablet tooling like the aforementioned Stokes used for digoxin manufacture.



(Ref: Remington: The Science and Practice of Pharmacy, 19th Edition, 1995, Mack Publishing, Easton, PA)

Multiple upper and lower punches as well as the dies are shown. Additionally the machine location (weight cam), which establishes the amount of material, which flows into the void made by the lower punch and the die, is shown (fill). The weight cam adjusts the setting of the lower punch penetration into the die. This cam may be adjusted up and down thereby changing the penetration of the lower punch and subsequently the available volume for the blend. The result of this adjustment allows a tablet of the desired weight to be compressed. Once the die is filled, the upper and lower punches travel under the pressure rollers, which allows the upper punch to enter the die and reduce the volume available to the blend subsequently forming a tablet. The tablet is ejected (ejection cam) by being pushed out of the die by the lower punch.

This punch movement is accomplished by the machine turret, which rotates the punches and dies over a set of cams and tracks, which guide the punches to the locations shown in the schematic. It should be noted that in the case of the Stokes machines used for Digitek there are two sets of upper and lower punch rollers (front and back) which allow for increased tablet output for the equipment. The mechanics of these rollers are identical. The set up in this case requires that adjustments be made to the

front and back weight controls to assure identical tablet specifications are maintained by both compression stages.

The compressed tablets that come off of the tablet press are then fed through a tablet de-duster as well as a metal detector for dust removal and identification of potential metal fragments. The tablets are collected in labeled bulk storage containers / buckets for transfer to the packaging operation.

We did not consider the sample frequency (every hour) used during the compression phase of the manufacture to be adequate. Based on our experience plus the fact that two machines are in use as well as the amount of material being produced it is difficult to rationalize this sample frequency. One could envision the various problems that can occur in the space of one hour.

Packaging

During the packaging operations the personnel operating the tablet counter saw an over size or "double thick" tablet in the feed tracks of the tablet counter (MTC12). The batch was completed using an extra degree of caution with attention paid to the identification of any additional over-size tablets presenting themselves in the counter tracks. As best as we can determine, there were a total of 5 tablets discovered in this situation as noted on page 2759 for batch 70924A.

Investigation Report

This event resulted in an investigation being opened to determine the root cause of the over size tablets. In addition, the batch was dumped back (removed from the finished packages) for a visual inspection of the entire batch. The investigation report (page 3319-3320) noted that a total of 15 tablets were discovered during the 100% visual inspection.

The investigation report goes on to note that a potential root cause for the occurrence of the thick tablets may be an artifact of the compression machine start-up procedure. This is credible since it is known that to achieve a set series of specifications (weight, thickness and hardness) the mechanics of centering the adjustments will create thick tablets. These over-size tablets are normally captured and discarded.

A potential problem could occur if where these over size tablets may hang up in the tablet de-duster or metal detector. This becomes more likely should the operators fail to remove the de-duster and the metal detector during start up and adjustment. The report goes on to note that as a preventive action the operators were instructed to remove the de-duster and the metal detector during the start-up and the pieces are only to be replaced after the desired specifications have been achieved. This would suggest that these precautions were put in place after the manufacture of batch 70924A.

Commentary on the Investigation

The factors noted during the investigation while relevant to batch 70924A fail to address aspects which must be considered as a continuum with regard to the life cycle of the Digitek product line. This is said in light of the apparent absence of an evaluation of Digitek 0.125mg batches manufactured prior to and after batch 70924A. It has been our experience that it is industry practice to expand technical investigations to address the issues surfaced during the current investigation as a means to probe the technical soundness of decisions made with follow on batches as well using prior batches as a source of guidance for aiding the current investigation.

We were not able to find either the assay or dosage form weights of the offending (over size) tablets as a part of the investigation report. This makes any subsequent evaluation of the data difficult since the nature of the over-size tablets is unknown. This would include the digoxin content of the over-size tablets. This knowledge would allow an estimation of the nature of the additional materials comprising the over-size tablets. The lack of data for the over-size tablets is something that in our opinion is a major flaw in the firm's approach to addressing product problems. It is also taken as indicative of a lack of rigor when addressing product problems in particular when dealing with products having the potency of the API in question.

In the absence of such quantitative information one needs to rely on the observations contained in the records. The recorded observations when considered against a theory that such a tablet would have been randomly produced during the normal manufacture of the tablets is without merit. This is said since the records show only machine stops and re-starts for routine events with the exclusion of the punch cleaning mentioned. This in itself would not support the random compression of an over-size tablet. It would, however, lend credibility to the proposal that the re-start of the machine is a potential source of over-size tablets, which are an artifact of the adjustment procedure (weight, hardness, thickness).

To focus on the potential of tablet carry over by a punch to allow it to be re-compressed with an additional fill amount is unlikely in our experience. This is based on the nature of the Digitek composition as well as the unlikely event that such an event would go unnoticed by the operators.

Compression machines are equipped with an over-load mechanism that is designed to protect the punches. This over-load is mechanical and responds to applied force s, which exceed the established rating set on the equipment. Should the void space (made by the lower punch and the die) be over filled by the blend and a tablet stuck to a punch the system would react to the over-fill by making a distinctive pounding noise. This is something that would not escape the notice of a trained operator. This would also be an event that had taken place at least 20 times (the recorded number of over-size tablets) through out the batch. When this fact is combined with the weight, thickness and hardness settings (mid to upper range) recorded for Digitek the likelihood of this event occurring periodically through out the batch without notice would be small.

The sample frequency of every hour is not addressed and this should be addressed in the report. The need for vigilance during the compression operation cannot be underestimated. Assuring the batch of tablets meets in-process specifications is a primary objective. The presence of a trained operator also assures that the machine is running as expected. The protracted sample frequency being used would suggest a lack of batch oversight in the case of digoxin tablets.

General Overview

What is blending and blend uniformity?

This is the bringing together of the materials (API and inert) needed to realize the manufacture of a solid oral dosage form like Digitek. The objective of blending is to render a homogeneous mass which when randomly sampled those subsequent samples would possess the same composition as the continuous mass from which it is taken. Simply stated this means that the tablet content uniformity will be reflective within an expected degree of variation to that of the powder mass prepared.

There are several types of blending mechanisms. There are also various blending equipment, which are made to accomplish the task of powder mixing. For the most part the use of diffusional blenders is a common approach for powder blending of pharmaceuticals. The diffusional blenders used are v-shaped, bins and double cone. The geometries of these are different but the mechanisms of mixing are similar. These blenders rotate in order to allow the powder within to move and thereby create a degree of flow, shear and particle interaction to achieve a uniform blended powder mass.

The type of blending mechanism we would expect to be reflective of the process used for Digitek would be one of cohesive blending. This means that the powders, which are to be used, are cohesive or lumpy and must be broken up during the blending. This is accomplished by the use of the intensifier bar within each blender used for Digitek. This allows the API to distribute within the powder bed comprised of the other inert ingredients

(Ref: J.T. Carstensen, "Pharmaceutical Principles of Solid Dosage Forms" pages 17 - 29, 1993, Technomic Publishing, Lancaster, PA).

The process of geometric dilution is another technique which may be employed in a blending process. This means that the blend is made in progressively larger volumes to allow for uniform distribution of the material through out the entire blend.

The one aspect that is not fully understood is the scale factors that allow the scale-up of products from laboratory scale to commercial scale. These are aspects that must be addressed using equipment supplier experience, product knowledge acquired during development, and experiments to determine the homogeneity of the desired final blend.

One commonly applied rule that is adhered to in general through out industry is to not change the geometry or shape of the diffusional blender during scale-up. This can result in unexpected problems and it is not uncommon to see development laboratories with an entire series of either bin or v-shaped blender sizes.

We noted during our review that the digoxin process uses two v-shaped blenders during the initial steps of the process. The final step of the process uses a double cone blender. This final step blender is of a different in geometry. It is our experience and is well documented that a change in geometry imparts increased product variability. This blender change combined with the firm's practice of discharging the final blend into drums suggests a process that lacks refinement respect to assuring the homogeneity of the powder blend form batch to batch of digoxin tablets.

(Ref: M. Levin Editor, "Pharmaceutical Process Scale-Up" pages 115 – 132, 2002, Marcel Dekker, New York)

The evaluation of blend uniformity is a difficult task and one that requires a rigidly established plan for removal of samples from the mixing vessel. This plan involves the proper selection of a suitable sampling device. This device is referred to as a thief and it allows a sample probe to be inserted into various locations in the blender. The pattern for the sample selection involves a careful determination of location as well as the top middle and bottom of the blend mass at each of these locations. The size of the samples to be removed are defined by FDA guidance and are usually weight multiples of the final dosage form. For example if the finished tablet will weight is 100mg then the sample should be within a range of 200-210mg. The desired state would be to have a sample that is the exact weight of the final product but the materials, equipment and procedural issues being used may obviate this objective. In the product reviewed the sample size was in the range of 220 – 260mg for a final tablet having a weight of 105mg.

In addition to the sample removal the transfer of the sample to the testing vessels for assay also poses a hurdle that necessitates careful technique to assure the sample weight is maintained during this transfer operation. A faulty technique during sample preparation will result in data that are not reliable and are not reflective of the homogeneity of the blended mass.

The reliability of sample data from the blend is critical to assuring the downstream product meets all quality attributes. In our review it is clear that the firm struggled with this procedure. Repetitive failures at the same blender location are not addressed nor are these anomalies discussed and clarity provided. Lacking this record it is our opinion that the blend sample program was ineffective and not predictive of final product quality.

The following quote is taken from Remington: The Science and Practice of Pharmacy, 19th edition page 1627, 1995

"Recently many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as "forgiving" as were the older wet-granulated products. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations."

This means that the drug or API used for the product must be well characterized and understood. We did not see any data that indicated the firm did any physicochemical review of the drug in problem batches. This lack of rigorous investigation is critical to assuring "fit for purpose" nature of the drug particularly when it is manufactured in a dry blend process.

What is Compression?

Tablets are the most commonly manufactured type of solid oral dosage form. Tablets are formed by the compression of free flowing granular material. The need for the material to be free flowing is to permit proper filling of the die prior to the application of force. The force applied causes the powder within the die to re-arrange physically and consolidate into the reduced volume that is created by the approach of the upper and lower punch. As the volume continues to be reduced the material undergoes a molecular re-arrangement that is often referred to as "cold welding". This results in the formation of bonds between the molecules of the material and creates a solid monolithic form. This solid form is then ejected from the die by the lower punch.

(Ref: M. Celik, Drug Development and Industrial Pharmacy, p. 767-810, 1992)

The key aspect of tablet manufacture is to establish a process which allows a uniform product with respect to assay / drug content and physical properties (thickness and hardness). The physical properties allow the tablet to be packaged and maintain an elegant form for the patient. The uniformity assures that the patient will get the dose as specified on the product label.

The attributes of the tablet are maintained during manufacture by taking regular samples and checking conformance to established tablet specifications (weight, thickness, hardness) through the entire batch run. Tablet weight assures the proper level of API is contained within each tablet, the thickness and hardness assure proper application of the amount of force to form the tablet. Hardness and thickness are also predictive of how well the tablet will respond to packaging and handling during shipment.

There are compression machines which are equipped with an internal force / pressure* monitoring system. These systems are commonly referred to as weight control systems. They take advantage of the mechanics involving the material filling the die and the subsequent entry of the upper punch to reduce the available volume. In this case should the material contained within the void space of the die and the lower punch exceed the amount which has been manually set by the operator the subsequent increase in force due to the excess material would cause the over-load system to react. This is a result of

the available volume becoming too small for the established space for the lower punch entry.

Compression machines that are equipped with weight control have the ability to measure the applied force by the upper punch by transducers attached to the pressure roller system. Should the set force limit on the monitoring system be exceeded several events take place. First the system automatically rejects the tablets resulting from the compression event that exceeded the set pressure limit. These tablets go to waste and are not part of the finished batch. Second the system automatically adjusts the weight cam. In other words it reduces the amount of material allowed to fill the void space. This automatic adjustment allows the weight of the tablets to be re-centered to the desired weight limits for the product being manufactured. The Stokes compression machines used to make batch 70924A were not equipped with automatic weight control but relied on operator monitoring and specification checks every hour.

(Ref: J. Swarbrick Editor, "Encyclopedia of Pharmaceutical Technology", Second Edition, pages 2669-2688, 2002)

**The terms pressure and force have been used interchangeably in several cases in this report. The term force is the exact terminology to be used when discussing compression of events. While this is a key academic point we have taken some literary license when describing tablet manufacture in this report. The rationale here is to allow the reader to clearly relate the terms presented in the schematic of the rotary tablet machine provided here.*

Formulation and Process

These aspects of the drug, inert ingredients and the process are defined during the development for the product. Part of this development requires that the API in question be compatible with the excipients to be used in the final dosage form. This is determined during a pre-formulation phase. This determines if the combination of inert and API is stable.

The reason the excipients are used is two fold first to achieve the correct dose by dilution of the API and second they allow the blend of API to flow and subsequently be compressed into tablets. Direct compression blends must have materials which allow flow these are lubricants and glidants such as stearic acid and colloidal silicon dioxide. There are materials that are capable of forming a solid during compression such as microcrystalline cellulose. Since the tablet must dissolve / disintegrate in the patients stomach disintegrants are added to help release the API. These materials include pregelatinized starch, croscarmellose and corn starch. Color may also be added for identification or marketing purposes.

Dry blends also require a material that will act to capture the API during blending and help it to distribute through the powder blend. Excipients such as corn starch are effective in achieving this key function. The main point to be taken here is that the inerts must be selected using the API characteristics as well as thereby making the properties of the drug critical to manufacturing a product which meets all quality attributes.

Conclusion and Observations

The drug digoxin is a potent compound with a well-established history of having a narrow therapeutic index. The data for digoxin manufacture that we reviewed show a lack of appreciation of the dangers of this compound. Product problems that were seen were not addressed with the scientific rigor, which in my opinion would be expected in this situation.

The firm lacks the fundamental understanding of the need to define the requirements of the product to be manufactured and take actions within their supply chain as well as within the manufacturing unit to consistently realize a quality product in the case of Digitek.

Some specific points are listed here:

- Blend homogeneity problems are seen during the testing of various batches. These problems varied in nature but were attributed to analytical testing errors and sample manipulation and recovery from the blending process. It is our experience that blend sampling and testing are difficult. This appears to hold in this case as the data reviewed would support the firm struggled with this task and did not resolve the problems as repetitive failures were noted.
- We do not consider the sample frequency (every hour) used during the compression phase of the manufacture to be adequate. Based on our experience hourly monitoring will not capture machine problems that would result in product defects that could be avoided.
- The over-size tablet investigation report notes that a potential root cause for the occurrence of the thick tablets may be an artifact of the compression machine start-up procedure. This is credible since it is known that to achieve a set series of specifications (weight, thickness and hardness) the mechanics of centering the adjustments will create thick tablets. These over-size tablets are normally captured and discarded. This indicates a lack of adherence to procedures during operations.
- The over-sized tablet report goes on to note that as a preventive action the operators were instructed to remove the de-duster and the metal detector during the start-up and the pieces are only to be replaced after the desired tablet specifications have been achieved. This indicates that these precautions were put in place after the manufacture of batch 70924A.
- The factors noted during the investigation while relevant to batch 70924A fail to address aspects which must be considered as a continuum with regard to the life cycle of the Digitek product line. This is said in light of the apparent absence of an evaluation of Digitek 0.125mg batches manufactured prior to and after batch 70924A. It has been our experience that this failure to investigate further brings into question a systemic problem with the products within the product line.

- We were not able to find either the assay or dosage form weights of the offending (over size) tablets as a part of the investigation report. This makes any subsequent evaluation of the data difficult since the nature of the over-size tablets is unknown. This would include the digoxin content of the over-size tablets. The lack of data for the over-size tablets is something that in our opinion is a major flaw in the firm's approach to addressing product problems. It is also taken as indicative of a lack of rigor when addressing product problems in particular when dealing with products having the potency of the API in question.
- The sample frequency of every hour is not addressed and this should be addressed in the investigation report. The need for vigilance during the compression operation cannot be underestimated. Assuring the batch of tablets meets in-process specifications is a primary objective. The presence of a trained operator also assures that the machine is running as expected. The protracted sample frequency being used suggests a lack of batch oversight in the case of digoxin tablets.
- To focus on the potential of tablet carry over by a punch to allow it to be re-compressed with an additional fill amount is unlikely in our experience. This is based on the nature of the Digitek composition as well as the unlikely event that such an event would go unnoticed by the operators. This of course brings into question again the protracted sample frequency (hourly) used to monitor digoxin compression.
- We noted during our review that the digoxin process uses two v-shaped blenders during the initial steps of the process. The final step of the process uses a double cone blender. This blender is of a different in geometry. It is our experience and is well documented that a change in geometry imparts increased product variability. This blender change combined with the firm's practice of discharging the final blend into drums suggests a process that lacks refinement with respect to assuring the homogeneity of the powder blend from batch to batch of digoxin tablets.
- The reliability of sample data from the blend is critical to assuring the downstream product meets all quality attributes. In our review it is clear that the firm struggled with this procedure. Repetitive failures at the same blender location are not addressed nor are these anomalies discussed and clarity provided. Lacking this record it is our opinion that the blend sample program was ineffective and not predictive of final product quality.
- The Stokes compression machines used to make digoxin are not equipped with automatic weight control but relied on operator monitoring. It is our experience that a weight control system be used for highly potent products. The lack of this automatic system in addition to an hourly in-process testing frequency shows a lack of rigor by the firm during the manufacture of digoxin.

Submitted and prepared by,

Alessa Somma

Appendix A- Materials Reviewed

In addition to the materials listed in the preceding report, I have also reviewed the following:

Actavis Totowa LLC Timeline- Bates No.: ACTAV 000309763

CGMP statutes

Description of Amide Pharmaceuticals Manufacturing Facility (from ANDA)- Bates No. ACTAV000000417- ACTAV000000424

Methods for Drug Substance and Drug Products (From ANDA)- Bates No. ACTAV000000812- ACTAV000000902

Chart of Compliance Actions regarding Digitek- Bates No. MYLN 000929851- MYLN 000929853

FDA 483 Report to Little Falls -01/10/06-02/08/06- Bates No.: ACTAV 000028908-28914

FDA 483 for Little Falls 7/10/2006 - 8/10/2006 (FOIA Copy)

Establishment Inspection Report (EIR) for Little Falls -7/10/06- 8/10/06 (FOIA Copy)

08/15/2006 Warning Letter from Department of Health and Human Services to Divya Patel

11/17/2006 Letter from Nasrat Hakim at Actavis to FDA in Response to FDA 483 (FOIA Copy)

Final Corrective Action Memo (audit of regulatory status of Actavis) – Bates No.: MYLN 00030303- MYLN 0003030330307

02/01/2007-Revised Warning Letter- Bates No.: ACTAV000028242- ACTAV000028248

9/5/2007 - 9/28/2007- FDA 483 - Little Falls 2007 (FOIA Copy)

EIR 09/05/07-09/28/07 (FOIA Copy)

12/5/2007 Investigation of Deviation Report, Dig Product Lot #70924A1- Bates No.: ACTAV000003317-3336; ACTAV000002598- ACTAV000002622

Batch Record for # 07924A- Bates No.: ACTAV00002650 – ACTAV00002842

04/09/2008 Letter from Jasmine Shah to FDA re: change in QC lab and testing facility from Little Falls to Riverview – Bates No.: ACTAV000006485

3/18/2008 - 5/20/2008 FDA 483 - Riverview 3/18/2008 - 5/20/2008- Bates No.:
ACTAV000028225- ACTAV000028240

Establishment Inspection Report (EIR) for Little Falls 03/18/08 - 05/20/08; (FOIA Copy)

Investigation # 08-060 (re Batch # 80228A1)- Bates No.: ACTAV000928231

FDA Little Falls Inspection Closeout 05/20/08- Bates No.: ACTAV 000543001- ACTAV 000543002

07/21/08 Letter from FDA enclosing EIR for 05/21/08 Inspection- Bates No.:
ACTAV0000429520- ACTAV0000429535

08/15/08 Letter to FDA from Actavis Elizabeth from Anthony J. Delicato to Sarah Della Fave at
FDA

11/14/2008 Complaint for Permanent Injunction

12/16/2009 Deposition of Richard Dowling

1/18/2010 Deposition of Phyllis Lambridis

1/22/2010 Deposition of Daniel Bitler

1/25/2010 Deposition of Scott Talbot

Digitek Product Litigation Expert Witness Report

Dr. David M. Bliesner, Ph.D.

President

Delphi Analytical Services, Inc.

1. Purpose

This report is a thorough, detailed and independent review of the facts related to Digitek Product Litigation. In particular, this review was specifically conducted to determine if Amide Pharmaceutical, Inc. (which later became Actavis Totowa, LLC and referred to as Amide/Actavis within this report) demonstrated a systemic failure to implement quality systems which in turn created a high likelihood that adulterated drug product made it to the marketplace.

2. Background and Qualifications

Summary

My name is Dr. David M. Bliesner, Ph.D. I am President of Delphi Analytical Services, Inc. which is a private consulting firm that has been in business since February 1999. Delphi Analytical Service's mission is to improve our clients' level of compliance with the Current Good Manufacturing Practices (CGMPs) and Quality System Regulations (QSRs) by providing consulting services, instructional technology, instruction, and compliance products. Delphi's core competencies include (1) Quality Assurance auditing and process improvement (2) Developing and implementing corrective action plans especially related to FDA regulatory action including Consent Decrees (3) Instruction in CGMPs (4) Video-based learning software and online educational product development via our patent-pending process. Our clients include companies from the "top ten" list of pharmaceutical, biopharmaceutical, medical device, and contract analytical industries as well as smaller firms. I am also an Associate Professor at Saint Leo University, Saint Leo, Florida.

Education and Work History

I am a graduate of the United States Naval Academy Class of 1983 where I earned a bachelor's degree in chemistry which is certified by the American Chemical Society. I have a Ph.D. in Analytical Chemistry for the University of Vermont. My dissertation is titled "Chromatographic and Nuclear Magnetic Resonance Studies of Reversed Phase Liquid Chromatographic Interphases". I finished my Ph.D. studies in just under four years. I continue to be actively involved in education and training particularly in the field of CGMPs. I teach CGMPs and other compliance and related courses at client sites and international conferences. I develop and present new course materials and have produced video-based online instruction which I offer for sale via the internet. I am a published author of technical and compliance related articles and texts. I am sole



companies operating under consent decrees. This experience involved auditing, capturing deficiencies, and reporting final results. In addition, I also served as a corrective action verifier to certify that the companies have implemented valid systems-based corrective actions, that personnel have been trained on these actions, that the corrective actions are working and that there is data to support the verification. Some of my more recent assignments have included assisting a large Medical Device firm better understand and comply with the CGMPs and Medical Device Quality System Regulations (QSR) as they relate to submission of marketing applications for drug-medical device combinations. I am also helping a client establish a practical and efficient Out of Specification (OOS) investigation system, and helping another client by reviewing manufacturing and laboratory investigation reports.

Expert Witness Experience

This is my first expertise witness assignment.

3. Overview of the Current Good Manufacturing Practice Regulations and Quality Systems

The Essence of the Current Good Manufacturing Practice Regulations

The Current Good Manufacturing Practice Regulations commonly referred to as GMP, is the law. Codified in 21 Code of Federal Regulations (CFR) Parts 210 and 211. The GMPs were enacted by Congress and they are the regulations that "...contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess." (Reference: http://www.access.gpo.gov/nara/cfr/waisidx_10/21cfrv4_10.html, http://edocket.access.gpo.gov/cfr_2009/aprqt/21cfr210.1.htm).

In my experience, the purpose of the GMPs is to lay out the *minimum* standards required in order to insure drugs are safe, effective and have the properties promised by the manufacturer. The GMPs are not a "how to manual", but a starting point for manufacturers to produce safe and effective products. In addition, GMPs are most often referred to as Current Good Manufacturing Practices, cGMPs or CGMPs. The "C" in CGMPs means the best practices in the industry which, is currently being applied today. In my experience, FDA also recognizes industry standards and best practices and expects all manufacturers to operate at that level even if it is not spelled out specifically in the regulations.

When teaching CGMP compliance courses, I instruct my students that the essence of the CGMPs is captured in the following statement:

Compliance with Current Good Manufacturing Practices Means Showing you are
in Control of Your Operations

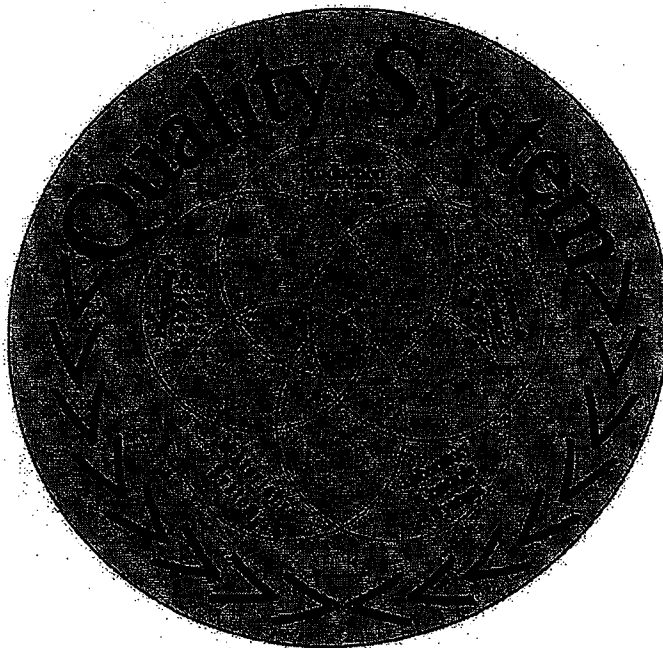
Therefore, if you are not in control of your operations you are not in compliance
with the regulations.

Quality Systems: The Best Way to Comply with the CGMPs

Activities found in drug firms are typically organized into six systems. These
systems are sets of operations and related activities and they include: (1) The
Quality System (2) The Facilities and Equipment System (3) The Materials
System (4) The Production System (5) The Packaging and Labeling System and
(6) The Laboratory Control System.

Control of all systems helps to ensure the firm will produce drugs that are safe,
have the proper identity and strength, and meet the quality and purity
characteristics as intended. (Reference: Guidance for Industry: Quality Systems
Approach to Pharmaceutical CGMP Regulations, September 2006
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/s/ucm064971.htm>)

A graphical depiction of these six systems is shown below:



Collectively, these six systems are referred to as Quality Systems. Compliance
with the CGMPs is typically accomplished by implementing a Quality Systems
based approach. Of particular note in this diagram:

- All six systems are integrated and intertwined with each other and do not stand alone
- Every drug product manufactured at a facility is impacted by Quality Systems
- If one of the systems is out of compliance then it impacts all drug products manufactured at the facility
- The Quality System (typically thought of as Quality Assurance) is the overarching system which impacts and encompasses the remaining five systems
- Failure of the Quality System (Quality Assurance) means all products manufactured, tested, packed and held are at risk of being adulterated.

In 2002 FDA began using a Quality Systems based approach in their assessment of drug firms by using Compliance Program Guidance Manual (CPGM) 7356.002 "Drug Manufacturing Inspections" as a guide during inspections. This document exists and is accessible to the public through the FDA website (Reference: <http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm#drugs>). FDA has used this document as a guide to inspect Amide/Actavis facilities since at least 2006 (Reference: See Attachment A18). In my opinion, this document is well known in the industry.

In addition to CPGM 7356.002, FDA also issued a Guidance Document in 2006 titled "Quality Systems Approach to Pharmaceutical Regulations" (Reference: See Attachment A12 and Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006 <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm>). The intent of this document is to help manufacturers implement modern quality systems to meet the requirements of the CGMPs. The guidance is not intended to place any new expectations on manufacturers or replace the CGMPs, but to assist them in compliance with the law. Where appropriate in this document, correlations between quality systems and the CGMPs are highlighted. In my opinion, this guidance is well known in the industry.

Of particular note, based on my experience, the 2006 Guidance Document for Quality Systems Approach to Pharmaceutical Regulations emphasizes the importance of leadership and management responsibilities in the proper implementation of Quality Systems. Leadership and Management responsibilities per say is not explicitly required in the CGMPs. However, modern robust quality system models call for management to play key roles in the design, implementation and control of the quality system. Therefore, Management Responsibility and Leadership are recognized as crucial and they represent an example of the "C" in CGMPs which are industry best practices. (Reference: See Attachment A22 and Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006 <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm>).

4. Review of Amide/Actavis Status of Compliance with CGMPs: My Approach

In order to accurately evaluate the status of Amide/Actavis's status of compliance with the CGMPs I took the following approach:

- Assumed Amide/Actavis was a new consulting client needing assistance with respect to determining their level of compliance with the CGMPs
- Performed a "Paper Audit" of the facility to determine past and current status of compliance with respect to the CGMPs. This audit included:
 1. Review of FDA actions including Form 483s, Warning Letters, Complaints and Consent Decrees, and Establishment Inspection Reports (EIRs)
 2. Review of Amide/Actavis responses to these actions
 3. Conducted "Interviews" of key personnel by reviewing records of depositions
 4. Review of Amide/Actavis internal documents, memoranda, standard operating procedures, and e-mails
 5. Review of customer internal documents, memoranda, and e-mails
 6. Review of the Abbreviated New Drug Application (ANDA) for Digitek
- Selected, collated and compiled a key documents list throughout the process
- Selected, collated, compiled an FDA actions list throughout the process
- Selected, collated and compiled a list of facts regarding Digitek tablet manufacturing
- Presented key documents in tabular format
- Presented FDA actions in a tabular format
- Presented facts regarding Digitek tablet manufacturing in list format
- Wrote this report using information extracted from all these documents, tables and lists
- Referred to both document tables and lists as needed

It should be noted that I have reviewed over 8,000 pages of documents in order to generate this report. In addition, should additional information become available for my review I reserve the right to supplement my opinions based on the new information.

References used to make my conclusions are listed in Attachment A: "Selected Reference Documents for Digitek CGMP Compliance Review-Approximate Chronological Order" and Attachment B: "Summary of Some FDA Actions: Amide Pharmaceutical, Inc., Actavis/Amide". In addition, I have compiled a

document called "Some Facts Regarding Digitek Tablet Manufacturing". It is included below as Attachment C.

5. Summary of Actions Taken by FDA against Amide/Actavis Pharmaceuticals

Amide/Actavis is a company with an extensive 27 year history of non-compliance with the CGMPs. which has led to repeated release of adulterated product to the marketplace.

The following is a summary of actions taken by FDA in an attempt to assist, prompt, cajole, and force Amide/Actavis to comply with the law:

FDA Action		Number of Occurrences	Description
FDA Form 483		26	First FDA Form 483 issued in 1983 during first FDA site visit; Last Form 483 issued in 2009. Most all Form 483s have numerous observations. (Reference: See Attachment A1, B46)
Warning Letters		6	These Warning Letters highlighted "Significant deviations from the Current Good Manufacturing Practice (cGMP) regulations set forth in Title 21, Code of Federal Regulations, Parts 210, 211, in conjunction with your firm's manufacture of prescription drug products". Reference: See example Attachment B32, B33)
Product Recalls		4	1990 Class II: Super or sub potent tablets due to thickness 1995 Class III: Incorrect package insert (a failure of packaging and labeling portion of the CGMPs) 2008 25 April, Class I Digoxin double thick or super potent 2008 1 August, total product recall

FDA Action		Number of Occurrences	Description
			from Actavis Totowa Little Falls , New Jersey Site, 66 products total. (Reference: See Attachment A49, A55, A63)
Consent Decrees		2	First Consent Decree signed in 1992 by Chandu Patel, 23 March 1992. Second Consent Decree signed in 2008 by Sigurdur Oli Olafsson and Douglas Boothe, 23 December 2008. (Reference: See Attachment B6, B45)

It should be noted, in my experience Consent Decrees are not common and mostly occur when a company has shown repeated and persistent non-compliance with the law.

Attachment B gives a more detailed description of the FDA actions summarized above and includes linkages to Plaintiff's Exhibits and FDA sources documents.

6. A Summary of Some Facts Regarding Digitek Tablet Manufacture and the Company's Chronic and Continuing Failures of Compliance with the Current Good Manufacturing Practice Regulations

Manufacturing and related activities for Amide/Actavis took place at three separate locations over the course of over 27 years. These include:

- 101 East Main Street, Little Falls, New Jersey 07424 (Little Falls)
- 990 Riverview Drive, Totowa, New Jersey 07512 (Riverview)
- 4 Taft Road, Totowa, New Jersey 07512 (Taft Road)

The majority of my observations however relate to the Little Falls, New Jersey facility however compliance issues exist at all sites as would be expected by multiple sites lead by the same management.

The following are some historical facts regarding Digitek tablet manufacturing presented in approximate chronological order:

1. Digoxin has been used as a heart drug for over 230 years. Digoxin tablets have been on the market in the United States since 1938. (Reference: See Attachment A69)

2. Digoxin has a narrow therapeutic index which means that a very narrow range of concentration in the bloodstream must be maintained or toxicity or lack of effect can occur. (Reference: See Attachment A69)
3. Difficulty in manufacture of Digoxin tablets has been known for some time and a concern to FDA early on. This fact prompted Congress to pass the Digoxin Regulation in 1974 (21 CFR Part 310.500) which required manufacturers of Digoxin tablets to submit their products to FDA for certification. (Reference: See Attachment A10)
4. June 1995 FDA issues certification to Amide Pharmaceuticals allowing them to manufacture and sell Digoxin under the Batch Certification Regulation 21 CFR 310.500. (Reference: See Attachment B11)
5. Continued product safety concerns by FDA prompted the repeal of 21 CFR 300.15, thus requiring the submission of an NDA by the product innovator Burroughs-Wellcome, which was approved in 1995 with the trade name Lanoxin. (Reference: See Attachment A10)
6. During the same period, Amide executed an extensive year long product development effort to formulate, manufacture and collect data to support submission of an ANDA for Digoxin tablets, thus confirming the concern FDA has with respect to the difficulties associated with manufacturing Digoxin tablets. Amides efforts resulted in at least 40 to 50 experiments before the proper formulation was achieved. (Reference: See Attachment A7)
7. Process validation which was included in the ANDA application for Digoxin tablets occurred in mid-November 1997. Process validation did not include all strengths of the product. Process validation was performed only on 0.250 mg strength tablets. The .250 mg tablet is white and does not contain colorant. The 0.125 mg tablet is green and the 0.500 mg tablet is yellow. (Reference: See Attachment A8)
8. Successful formulation of Digoxin tables required micronization during product manufacture. Micronization is the process of transforming active ingredient and/or excipients into a fine powder. Fine powders led to problems with static electricity during manufacturing especially during the winter months. (Reference: Attachment A7, A34)
9. On 21 February 2001 the Law Firm of McKenna & Cuneo, LLP of Washington DC argued on behalf of Bertek Pharmaceuticals and Amide for revocation of the 1974 Digoxin Regulation (21 CFR Part 310.500) to "...ensure that the marketplace does not include Digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence,

formulation and manufacturing changes that have not been approved by FDA and unproven labeling claims". (Reference: Attachment A10)

10. Amide first experienced difficulties with FDA from 28 July to 9 August 1983 during its first inspection shortly after the Little Falls, New Jersey facility opened. Major findings included:

- a. Stability testing program didn't support 2 year expiration
- b. Control of labels was inadequate
- c. Personnel making unauthorized changes to batch records
- d. Unaccounted loss of material during manufacture of tablets

(Reference: Attachment B1)

11. From September 1984 to March 1989 (~5 ½ years) FDA inspections of Amide at Little Falls finds repeated, significant violations of the CGMPs. Major findings include:

- a. Insufficient methods validation
- b. Unsound methodology
- c. Inadequate review of data
- d. Improper calibration practices
- e. Poor record keeping
- f. Lack of submission of periodic reports on ANDA products,
- g. Insufficient stability data

(Reference: Attachment B1, B2)

12. December 1990 Class II recall initiated for variation in tablet size resulting in sub and super potent drug product, demonstrating lack of manufacturing controls since at least this time. (Reference: Attachment B5)

13. First Consent Decree of Injunction signed by between Chandu Patel, President, Amide Pharmaceutical, Inc. and US Justice Department. Specific points FDA required by include:

- a. QA personnel must be adequate in number and have background, education, training, experience or combination therein
- b. QC (laboratory personnel must be adequate in number and have background, education, training, experience or combination therein
- c. All laboratory and analytical procedures shall be validated
- d. Laboratory practices shall reflect actual written SOPs and be followed
- e. Records required by GMPs shall be kept and recorded at the time events occurred
- f. Validations to be reviewed by third party
- g. Laboratory instrument procedures to be reviewed by third party

- h. Laboratory analyst shall be trained by third party for each type of instrumentation
- i. Manufacturing methods, facilities and controls to be reviewed by a third party
- j. All products to be certified by third party
- k. Third party to certify to FDA all actions have been taken

(Reference: Attachment B6)

- 14. From 23 March 1992 until 10 June 2002 Amide is frequently inspected by FDA under terms of the Consent Decree and for ANDA Pre-Approval Inspections. FDA writes numerous Form 483s with multiple observations. FDA denies Amide request to lift the Consent Decree on at least three separate occasions. (Reference: Attachment B6-B10, B13-B19, B21-B23)
- 15. 10 August 1995 Class III product recall initiated by Amide for incorrect package insert. (Reference: Attachment B12)
- 16. October 1997, Amide submits ANDA to produce Digoxin tablets using process validation data generated in 1994. (Reference: Attachment A8)
- 17. Amide receives approval from FDA to manufacture and sell Digoxin Tablets on 23 December 1999. (Reference: Attachment B20)
- 18. 9 May 2000, Adverse Drug Event for Digoxin reported to Amide: Death Occurs 2.5 hours after taking Digitek. Event not reported to FDA. (Reference: Attachment A9)
- 19. 29 October to 29 November 2001, FDA inspects Amide and makes the following Form 483 observations:
 - a. Thin tablets observed by packaging personnel
 - b. Visual inspection resulted in rejection of 1,600 tablets
 - c. FDA states no assurance that all short weight/thin tablets were rejected
 - d. No written rework procedure in place
 - e. No assurances that all 32 stations of tablet press yields tablets within specification for weight or thickness because only 10 of 32 stations were checked during operational/performance qualification studies and compression start-up.

(Reference: Attachment A11)

- 20. FDA Form 483 Observation for the 29 October to 29 November 2001 states:

“During the packaging of [redacted] thin tablets were observed by packaging personnel. A portion of the batch (drum 4, 7, 8, & 11) was visually inspected

for the presence of thin tablets, which resulted in approximately 1,600 tablets being rejected and ultimately the rejection of drums 4, 7, 8 and 11. The entire contents of drum 1,2,3,5,6,9 and 10 were packaged. During packaging, the packaging line was run at slower speed so that thin tablets could be observed on the tracks.

- There is no assurance that all short weight/thin tablets were rejected from the batch
- There was no rework procedure written for the tablet inspection of drums
- During operational/performance qualification studies from compression start-up, 10 & 32 stations of the tablet press are checked for weight and thickness. Therefore, there is no assurance that all 32 stations of the tablet press yield tablets within specifications for weight and thickness”

As part of their response to FDA, Jasmine Shah, Director of Regulatory Affairs states:

“In order to handle this type of problem in the future, Amide has purchased tablet sorting equipment that will sort thick/thin tablets. Enclosed is a purchase order copy for the equipment (Attachment 1). Upon receipt of the equipment, an IQ/OQ/PQ will be performed and the equipment will be used if such a situation arises.”

(Reference: A11, Plaintiff's Exhibit 236)

21. 10 June 2002, FDA lifts first Consent Decree (Reference: Attachment B23)
22. 8 June 2004 Amide receives complaint from a pharmacist in Bellingham, WA regarding thick Digoxin tablet. Amide confirms double thickness, no definitive root cause found. Compression occurred on tablet presses #67 or #71. Tablet manufacture occurred 6, 7 and 10 November 2003. No chemical testing conducted on product. This is the first instance of double thick Digoxin tablets reported and confirmed in market place. (Reference: Attachment A13, A14)
23. December 2003 Sigurdur Olafsson is made Managing Director of Actavis US. (Reference: p 24, Sigurdur Olafsson deposition 10 February 2010)
24. 16 July 2004 Sigurdur Olafsson begins conducting due diligence review of Amide for potential purchase by Actavis hf. He finds no problems with respect to FDA or compliance with CGMPs. (Reference: Plaintiff's Exhibit 190)

25. Formal due diligence conducted by Actavis for purchase of Amide Pharmaceutical, Inc. from July 2004 to July 2005. According to CEO Sigurdur Olafsson, outside consultants used for detailed due diligence consisting of an operation team and a quality team. No problems with respect to FDA or compliance with CGMPs. (Reference: p 50-52, Sigurdur Olafsson deposition 10 February 2010)
26. Actavis purchases Amide Pharmaceuticals on 27 July 2005. Purchase includes Little Falls Facility (main site), Taft Road Facility and Riverview Facility all within close proximity to one another. Little Falls is the original facility where most of the manufacturing and compliance related difficulties occurred. (Reference: p 24, 225 Divya C. Patel deposition 30 April 2010)
27. 15 May 2006, company named changes from Amide Pharmaceutical, Inc. to Actavis Totowa, LLC following sale to Actavis Group, hf. (Reference: Plaintiff's Exhibit 91)
28. January 2006, Sigurdur Olafsson is made President of Actavis US. (Reference: p 62, Sigurdur Olafsson deposition 10 February 2010)
29. 10 January 2006 to 8 February 2006 FDA inspects Actavis Totowa, Little Falls, New Jersey and writes a Form 483 with 8 observations. Inspection is primarily related to pharmacovigilance. Specifics include:
 - a. Adverse drug experiences not reported to FDA within proper time frame or not reported at all, including Death Associated with Digitek on 9 May 2000 2.5 hours after taking Digitek
 - b. No review of literature related ADE for products
 - c. No written procedures for ADEs
 - d. Failure to investigate consumer complaints including a metal screw found in a bottle of product
 - e. Failure to investigate OOS percent yield of bulk material
 - f. No process validation
 - g. Qualification and start-up procedures in manufacturing is inadequate(Reference: Attachment A16)
30. In e-mails from Ashok Nigalaye to Divya Patel and from Ashok to Bharat Patel dated 12 July 2006 and 21 July 2006. Discussion about purchasing new tablet presses which contain tablet weight and thickness controls, including an equipment quote #26943 from DLS Enterprises. (Reference: Plaintiff's Exhibit 258 and 259)
31. 10 July to 10 August 2006, FDA inspects Actavis Totowa, LLC Little Falls, New Jersey. Inspectional coverage includes the Quality System, Laboratory Control System and Material System. FDA's summary statement pronounced:

“A review of the firm’s manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented.”

A Form 483 was issued with 15 observations which included:

- a. 1-The Quality Unit Lacks authority to fully investigate errors that have occurred.
- b. 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing
- c. 3- The responsibilities and procedures applicable to the quality control unit are not fully followed
- d. 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications
- e. 5- Input to and output from the computer are not checked for accuracy
- f. 6- The suitability of testing methods is not verified under actual conditions of use
- g. 7- The written stability testing program is not followed
- h. 8- Examination of testing samples is not done to assure that in-process materials conform to specifications
- i. 9- Deviations from written procedures and process control procedures are not recorded and justified
- j. 10- Master production and control records are deficient in that they do not include complete sampling and procedures
- k. 11- Equipment used in the manufacture, processing, packing, or holding of drug products is not of appropriate design to facilitate operations for intended use
- l. 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product
- m. 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable
- n. 14- Written procedures are not followed by receipt and storage of components
- o. 15- There was a failure to handle and store components at all times in a manner to prevent contamination

Divya Patel is still the most responsible person on site, Jasmine Shah is still primarily responsible for Quality Assurance and Regulatory Affairs, and Dan Bittler is still primarily responsible for Quality Assurance approval and sign-off. These observations are similar and consistent with what FDA has found since its first observations starting in 1983.

(Reference: Attachment A18)

32. 15 August 2006 FDA issues Warning Letter to Actavis Totowa, LLC Little Falls New Jersey regarding inspection conducted 10 January 2006 to 8 February 2006. (Reference: Attachment A19)

33. 4 January 2007 Mylan Pharmaceuticals, Inc. openly states reservations about continued relationship with Actavis:

"I believe that we should seriously consider looking at either manufacturing the product here or as an alternate site to Amide"

(Reference: Attachment A24)

34. 1 February 2007, Warning Letter issues to Divya Patel concerning 10 July to 10 August inspection findings. (Reference: Attachment A25)

35. Actavis annual product review for Digitek 0.25 mg tablets on 3 April 2007 for 1 December 2006 to 31 December 2006 finds the following:

- a. 17 Adverse events were noted including some for
 - i. Atrial fibrillation
 - ii. Elevated Digoxin level in blood
 - iii. Orthostatic hypotension
 - iv. "Unknown" potency question
- b. Detail of investigations was limited due to inability to trace product in market to lots produced at plant
- c. One lot, 60319A Final Blend Assay Standard Deviation was 4.5% which was higher than other batches
- d. Some additional Content Uniformity and Dissolution vales were "slightly higher" compared to other batches reviewed.

(Reference: Attachment A27)

36. Blend uniformity failures for different products are discussed in an e-mail from Wanda Eng to Apurva Patel dated 20 July 2007. In particular, Blend Uniformity failures for Digoxin Tablets manufactured on 17 January 2007 and 12 March 2007 are discussed. One lot was rejected after additional testing and one was released. (Reference: Plaintiff's Exhibit 183)

37. 5 September 2007 to 28 September 2007, FDA inspects Actavis Totowa Little Falls, NJ facility as a follow-up to Warning Letter. It is a general GMP inspection and a pre-approval inspection for one product. Summary of findings include:

- a. An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning failure of one or more

- distributed batches of drug to meet the specifications established for it in the application (stability failure)
- b. Written stability testing program is not followed (36 month pull not tested for four products)
- c. Written production and process control procedures are not followed in the execution of production and process control functions (DOP #0033 Investigations of Out of Specification Results and DOI # QC-059 are not followed)

(Reference: Attachment A29)

38. 1 October 2007 internal e-mail indicates Digoxin 0.25 mg is the top product where Adverse Drug Events are associated with death or permanent injury. (Reference: Attachment A30)

39. 30 November 2007, Double thick tablets discovered during manufacturing of Digoxin 0.125 mg tablets. Although initially halted, production continued following only visual inspection. Detailed investigation conducted within a very short period of time. Product is released to market without conclusive evidence of what caused the double thick problem on 5 December 2007. No chemical testing of tablets was conducted. (Reference: Attachment A31, A32)

40. Last quarter 2007 Digoxin Blend failure investigation conducted. Potential causes cited include:

- a. Blend sampling procedures (change over to slugs)
- b. Low humidity/high sampling
- c. API particle size
- d. Batch record problems
- e. Method issues
- f. Product validation
- g. Laboratory testing

According to company document, relative humidity levels were lower for months of October through April. Dryer conditions may lead to electrostatic attractions which may be the cause for the higher number of blend failures. (Reference: Attachment A34)

41. In an e-mail dated 18 December 2007, Richard Dowling states to Bharat Patel:

“As part of the corrective action for investigation number 07-093 for Digoxin double tablets, I am going to state that we will buy a complete set of lowers and dies for both strengths of Digoxin that will be dedicated and not used for any other products. It is possible the tablet stuck to the punch and was double compressed”.

(Reference: Plaintiff's Exhibit 97)

42. From 18 March to 20 May 2008 FDA conducted an inspection of the Actavis Totowa new Riverside facility located at 990 Riverview Drive, Totowa, New Jersey. According to the FDA:

"This inspection was limited to coverage of the Quality System due to significant cGMP deficiencies including but not limited to out of specification in-process, finished product and stability results for more than [redacted] prescription pharmaceutical products; release of Digoxin Tablets 0.125 mg, lot# 70924A2, following visual inspection of the [redacted] to remove "double thick" tablets; failure of the Quality Unit to reject products not meeting specifications, to complete Quality Assurance investigations, to expand investigations to other lots and products, to file NDA Field Alerts within timeframes, and to respond to out of specification products on the marketplace. Analytical methods requiring remediation remained in use and approximately [redacted] prescription drug products had no analytical evaluations of impurities on stability. Written procedures were not followed and changes with potential product quality impact were not all reviewed and approved by the Quality Unit. No market action was taken by the Quality Unit for any products on the market at the initiation of the inspection of the inspection despite confirmed out of specification, in-process, finished product and stability results. During the inspection, commitments to recall products were initiated based on inspectional findings. No comprehensive risk assessment or quality evaluation for all products on the market was conducted by the firm's Quality Unit prior to completion of the inspection. No additional systems were covered following the documented Quality System failure."

"Commitments to recall finished products from the marketplace were initiated on 4/09/08 and continued throughout the inspection for such products as Digoxin Tablets, Pentazocine and Nalaxone Hydrochloride Tablets, Carisoprodol/Aspirin/Codeine Phosphate Tablets, Hydrocodone Bitartrate and Homatropine Methylobromide Tablets and Mult-Bets pediatric prescription vitamins. However, there is no assurance of the strength, quality and purity of the approximately [redacted] of other products that remain on the market, all lots remaining in the two distribution centers, and the in-process products that remain at the firm's Little Falls, NJ and Totowa NJ locations. The products were manufactured, tested and released by the same Quality System".

(Reference: Attachment A37)

43. Actavis issues urgent recall notice to valued customers stating:

"This recall notice has been initiated due to overweight tablets."

(Reference: Attachment A35)

44. 25 April 2008 FDA and Actavis announce recall on all Digitek Tablets on the market. (Reference: Attachment B41)

45. On June 11 2008 Sigurdur Olafsson, now Deputy CEO, Actavis Group, CEO Actavis, Inc. issued response to FDA Form 483's generated during the 8 March to 20 May 2008 FDA inspection. He acknowledges most of the observations, but disagrees when he does not believe them to be correct. The following statement best captures his sentiment:

"It is quite fair to say, as we related to our April 2008 letter, that Actavis Totowa prides itself in maintenance of cGMP compliance by virtue of comprehensive and robust quality systems. Thus we were surprised and chagrined, as the last inspection developed, by our failure to have secured the compliance we had sought and committed to establish for Actavis Totowa."

(Reference: Attachment A61)

46. UDL Internal Investigation Record from March 2008 indicates "...one complaint for Digitek 125 mcg (#08-038) reported that the customer observed that the tablets appear smaller than usual and that her heart started racing". This observation was made in March before any recall announcement. (Reference: Attachment A36)

47. Actavis Investigation #08-060 for Digoxin Tablets 0.125 mg Lot # 80228A1, 1 April 2008. Overweight tablets were found during packaging. Preliminary investigation showed a 5000 count bottle had 17 out of 30 tablets above 120 mg. Put on hold pending QA investigation. (Reference: Attachment A39)

48. Actavis contracts Health Hazard Evaluation which is issued 18 April 2008. Conclusions:

"Double thick tablets could lead to digitalis toxicity; Can result in death. Thin tablets may cause congestive heart failure and arrhythmia."

(Reference: Attachment A40)

49. Mylan acknowledges Pharmacist identifying double thick products in market place (Reference: Attachment A58)

50. Actavis begins receiving a substantial number of complaints regarding Digitek (Reference: Attachment A59)

51. The management team responsible for all Operations, Administration and Quality at Amide was essentially the same for Amide since 1989 until 2008. These individuals include:

- a. Chandu Patel-President (~1984 to April 2003, Father of Divya Patel died, referenced within Divya C. Patel deposition 30 April 2010)
 - b. Divya Patel- President (1995 to April 2008, took over as President when father died in April 2003, reference deposition 30 April 2010)
 - c. Ashok Nigayale- R&D (June 1993 to January 2008, reference deposition 31 March 2010)
 - d. Jasmine Shah- Quality and Regulatory Affairs (1988 to August 2008 reference deposition 26 March 2010)
 - e. Dan Bitler- Quality Assurance (1995 to 23 May 2008 reference deposition 22 January 2010)
52. Ashok Nigalaye leaves company January 2008 (Reference: p. 29 deposition 31 March 2010)
53. Divya Patel leaves company April 2008 (Reference: p. 190 deposition of Divya Patel)
54. 27 April 2008 Mylan Chuck Koon in an e-mail to Hal Korman expresses concerns about Actavis problems with compliance being know "Well over a year ago." Also talks about how to get out of 10 year contract. (Reference: Attachment A56)
55. Sigurdur Oli Olafsson and Mark Keatley e-mail exchange on 2 May 2008, begins discussion of financial impact of problems associated with Digoxin production at Little Falls. Points include:
- a. What is FY 2008 revenue and gross margin for product?
 - b. Any deaths or injuries alleged against us?
 - c. Are we covered by insurance vs. product/process liability and Mylan liability?
 - d. Estimated recall cost only for this product
 - e. Need Digitek answers asap
- (Reference: Attachment A50)
56. Jeffrey Rope and Grudrun Eyjolfsdottir e-mail exchange on 3 May 2008 communicates equipment upgrades and concerns related to Digitek production which include:
- a. Have recommended purchase of 3-4 new PTK [tablet] presses with compaction force weight control and automatic reject.
 - b. Digoxin presses will be fitted with Kramer de-duster to protect operators from Digoxin tablet dust during packaging.
 - c. "In my view it is totally unacceptable that our people cannot read English operating procedures and batch records."

Jeffrey Rope confirms manufacturing people cannot read English and therefore cannot read operating procedures and batch records.

(Reference: Attachment A51)

57. In an e-mail dated 6 May 2008 from Mike Adams, Executive Director QA Compliance Mylan Pharmaceuticals to a large number of staff members, the following points were made with respect to the status of Digitek recall:

- a. "Actavis is setting up a process for consumers to obtain a blood test (through Quest)"
- b. "Actavis has addressed over 2,500 medical questions since April 25 2008"
- c. Total call volume to Stericycle since recall notice 128,768

(Reference: Attachment A59)

58. Actavis indicates plan to purchase new tableting equipment with weight controls (Reference: Plaintiff's Exhibit 140)

59. Dan Bitler leaves company 23 May 2008 (Reference: p. 16 deposition 22 January 2010)

60. Jasmine Shah leaves company August 2008 (Reference: p.8 deposition 26 March 2010)

61. 1 August 2008 Actavis and FDA announce voluntary recall of all products manufactured at Little Fall, New Jersey facility. (Reference: Attachment B43)

62. 14 November 2008 Complaint for Permanent Injunction United States of America vs. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe

(Reference: Attachment B44)

63. 23 December 2008 Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe.

(Reference: Attachment B45)

Please see Attachment C for a tabulated listing of these findings.

7. Root Causes for Amide Pharmaceuticals and Actavis Failure to Comply with the CGMPs Which Led to Release of Adulterated Product to Market

Following a thorough analysis of references cited in Attachments A and B the following root causes can be attributed to Amide/Actavis repeated failure to comply with the CGMPs which resulted in adulterated product to reach the market:

- **Lack of Leadership and Management Controls at All Levels Within the Organization**

(Reference: Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm> specifically pages 8-12)

- **A Lack of Quality Assurance Oversight**

(Reference: 21 CFR Sec. 211.22 (a))

- **A Poor Document Control System and Poor Documentation Practices**

(Reference: 21 CFR Sec. 211.22 (b))

- **Unqualified Personnel Serving in Various Positions of Management and in General Employment**

(Reference: 21 CFR Sec. 211.25)

- **Lack of a Proper Training and Qualification System for Employees at All Levels**

(Reference: Reference: 21 CFR Sec. 211.25)

8. Conclusions

The findings presented above are based upon existing, available documentation. From the review of these documents it is apparent that Amide/Actavis is a company with an extensive 27 year history of non-compliance with the CGMPs. It is my opinion to a reasonable degree of certainty that the systemic failure to implement quality systems and to comply with the regulations resulted in adulterated drug product making it to the marketplace.

9. References

See Attachments A through D below.

/s/ David M. Bliesner
Dr. David M. Bliesner, Ph.D.

Attachment A:**Selected Reference Documents for Digitek CGMP Compliance Review-Approximate
Chronological Order**

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
A1	Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Conducted 28 July to 9 August 1983	9 August 1983	Available through www.foiservices.com	<p>Form 483 is from initial inspection of Little Falls, New Jersey facility shortly after it was founded on 1 May 1983. Form 483 issued containing four observations. Specific statements of non-compliance with CGMPs include:</p> <ul style="list-style-type: none"> • Stability testing program doesn't support 2 year labeling • Label control system is inadequate • Unauthorized changes in batch records with no change in the master formula. • Loss of tablet cores not reconciled at completion of manufacturing
A2	Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Conducted 5 to 20 December 1989 and 2 to 15 February 1990	For 5 to 20 December 1989 and 2 to 15 February 1990	Available through www.foiservices.com	<p>FDA Summary of Findings states:</p> <p>"Inspection of this generic drug manufacturer was conducted to assess the firm's compliance with a voluntary agreement dated 4/20/89 under assignment #5260 (Exhibit 3A). Four DQRS reports, #77989,</p>

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	February 1990	inspection. Document Created after 15 February 1990		78686, 78013, and 79853, were covered under assignment #5672 (Exhibit 38). Also covered were assignment #5708, a GMP statutory obligation inspection, and assignment #6253 (Exhibit 3C), an HFD-341 request for a special investigation into the firm's compliance with the reporting requirements of 21 CFR 314.SQ(c)(2). Previous inspection of 3/26/89 et al was a follow-up to a violative inspection and found continued serious deviations. An injunction was recommended, and the voluntary agreement ensued. Current inspection found many previous deviations still existing in the laboratory including insufficient validation, unsound methodology, inadequate review of data, improper calibration practices, and poor record keeping. Deviations in other areas include the lack of submission of periodic reports on ANDA products, insufficient stability data for hydralazine HCl, the reuse of parchment paper for drying separate batches of product, and inadequate control of the incubator."
A3	Consent Decree of Injunction, Amide Pharmaceuticals, Inc. a Corporation and Chandu Patel, an Individual. Civil Action Number 92-513 Consent Decree of Injunction	23 March 1992	Provided by Miller Law Firm	This is a consent decree entered into by founder of Amide Pharmaceuticals and Department of Justice in March 1992. It is the result of continued failure to comply with the CGMPs even after efforts on the part of FDA to help Amide improve their compliance. Previous efforts included issuance of a memorandum of understanding which included a plan for improvement.

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				<p>Specific statements of non-compliance with CGMPs in the Decree include:</p> <ul style="list-style-type: none"> • QA personnel inadequate in number and have background, education, training, experience or combination therein • QC laboratory personnel inadequate in number and don't have background, education, training, experience or combination therein • Not all laboratory and analytical procedures validated • Laboratory practices don't reflect actual written SOPs and be followed • Records required by GMPs not kept and recorded at the time events occurred • Validations need to be reviewed by third party • Laboratory instrument procedures need to be reviewed by third party • Laboratory analyst need be trained by third party for each type of instrumentation • Manufacturing methods, facilities and controls to be need to be reviewed by a third party • All products need to be certified by third party • Data not properly recorded
A4	Establishment Inspection Report (EIR) for FDA	16 March 1994	Available through www.foiservices.com	This report was issued following an inspection conducted by FDA starting 16 March 1994. This

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	Inspection of Amide Pharmaceuticals, Inc. Inspection Conducted 16 March 1994			<p>inspection was a follow up to a previous inspection conducted 9 March 2003 which revealed the firm had not corrected some of the deficiencies previously cited and had not adhered to the terms of the consent decree. This particular inspection cited the following continuing CGMP issues:</p> <ul style="list-style-type: none"> • Failure to conduct retrospective or prospective process validation as committed to under consent decree nor demonstrated understanding of their importance • Methods not properly validated • Changes to methods not justified or validated • Cleaning validation studies not performed • SOPs were not consistently followed • QA approval not always gained before manufacturing process is initiated • Admission by Chandu Patel on large errors made by QA personnel • Blending process changes in the middle of validation batch production without investigation as to potential impact • Lack of control of contractors performing manufacturing steps • Loss of active ingredient during drying and final blending/compression without concern or explanation

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				<ul style="list-style-type: none"> • Products manufactured during validation lots without pre-determined acceptance specifications • Manufacturing investigations not complete and not appropriately documented • Black foreign material in final blend and finished product not adequately investigated <p>This EIR is very similar to the final EIR issued in 2006</p>
A5	Response by Jasmine Shah to Form 483 inspection observation by FDA: Poor Laboratory Practices for Digoxin Dissolution Testing	17 March 1995	Available through www.foiservices.com	<p>Letter by Director Regulatory Affairs to FDA District Office in Newark New Jersey addresses FDA 483 observation for inspection conducted on 16 March 1995 which stated "Poor laboratory practices were observed in the sampling of solutions from the dissolution apparatus during testing of Digoxin tablets batch 5069A and the resample of the batch." This is the first instance of Digoxin linked with FDA findings discovered in my review.</p>
A6	Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceuticals, Inc. Inspection Conducted November 1997	1 December 1997	Available through www.foiservices.com	<p>Inspection related to 1992 Consent Decree follow up- still significant GMP issues related to:</p> <ul style="list-style-type: none"> • Incomplete impurity profile testing on finished drug product • Failure to identify all known starting impurities • Inadequate cleaning validation • Failure to have SOPs for a wide variety of tasks

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				<p>including water sampling, validation data for hardness testing, HPLC data audit trails, adequate calibration and maintenance programs, etc.</p> <ul style="list-style-type: none"> • No stability data to support expiration dating for in-house standards • No environmental monitoring of warehouses • Laboratory analysts testing samples into compliance and not following OOS SOP • Inadequate alternate manufacturing procedures • No timeline for complete manufacturing investigations • Can track rejected product to destruction manifests.
A7	Deposition of Ashok Nigalaye, Ph.D.	31 March 2010 containing comments with respect to work done in 1999 or sooner	Made available through internet portal	<p>Deposition is in regard to Digitek product liability suit. The following points are extracted from Dr. Nigalaye's testimony:</p> <ul style="list-style-type: none"> • Dr. Nigalaye was the person who developed the Digitek formulation p.40 • He testifies that Digoxin has a narrow therapeutic index (e.g. have to control the level in the bloodstream) p.42 • He testified that there have been historical problems with formulating Digoxin in the industry at large. Consistent problems have existed in the past with respect to manufacture of Digoxin products. P.50-52

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				<ul style="list-style-type: none"> • Dr. Nigalaye testified that “.....we conducted at least 40 to 50 experiments before we came about this formulation” p. 96 • It took about a year to derive the current formulation of Digitek p.98 • He claims they have made “billions and billions without market complaints”. P.66 (NOTE: There is evidence to the contrary as per discovery of thick tablet by a pharmacist in 2004) • Dr. Nigalaye makes the statement “We had excellent results. We never failed for quality any batch in the lab.” P.115 NOTE: This is not true. There have been blend uniformity failures such as the “double think lot in November 2007” some of which were rejected for problems with blend uniformity. • He testifies that a pharmacist would notice “.....twice as thick as a normal tablet” p.118
A8	ANDA 40-282	December 1999	Made available through internet portal	<p>The following points have been extracted from the Digitek ANDA:</p> <ul style="list-style-type: none"> • Process validation occurred on 17 November 1994, five years before approval of ANDA • Process validation was performed on only the 0.250 mg dosage strength • The 0.250 mg strength does not have colorant. <p>Colors for the products are as follows:</p>

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				<ul style="list-style-type: none"> o 01.25 mg is green o 0.250 mg is white o 0.50 mg is yellow • Product is an immediate release dosage form as shown by PK profiles • Product is not granulated by mixed during manufacturing
A9	Adverse Event Not Reported to FDA (Included with Form 483 Observation Dated 8 March 2006)	Date of Event 9 May 2000 (Discovered by FDA 8 March 2006)	Within ACTAV00002891	Death in 2.5 hours after ingestion of first tablet.
A10	Comment to Docket Nos. 00N-169 and 00N-1610; Digoxin Products for Oral Use; Revocation of Conditions for Marketing and Reaffirmation of New Drug Status	21 February 2001	Plaintiff's Exhibit 232	On 21 February 2001 the Law Firm of McKenna & Cuneo, LLP of Washington DC argued on behalf of Bertek Pharmaceuticals and Amide for revocation of the 1974 Digoxin Regulation (21 CFR Part 310.500) to "...ensure that the marketplace does not include Digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence, formulation and manufacturing changes that have not been approved by FDA and unproven labeling claims". NOTE: Unapproved manufacturing changes are one of the consistent delinquencies reported by FDA of Amide.

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
A11	FDA Form 483 Observation from Inspection spanning Date 29 October to 29 November 2001 And Response by Jasmine Shah, Director Regulatory Affairs (Thin Tablets)	29 November 2001	Plaintiff's Exhibit 236	<p>FDA observed the following:</p> <ul style="list-style-type: none"> • Thin tablets observed by packaging personnel • Visual inspection resulted in rejection of 1,600 tablets • Packaging occurred at lower speed to detect additional thin tablets • FDA states no assurance that all short weight/thin tablets were rejected • No written rework procedure in place • No assurances that all 32 stations of tablet press yields tablets within specification for weight or thickness because only 10 of 32 stations were checked during operational/performance qualification studies and compression start-up. <p>In response to FDA Jasmine Shah states:</p> <ul style="list-style-type: none"> • Visual investigation was conducted • Stated thin green tablets would be easy to identify • As a precaution all drums were rejected • Conveyed to FDA that Amide purchased tablet sorting equipment (purchase order attached) • Rework procedure will be created <p>NOTE: No indication of sorting equipment in place during future operations.</p>

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A12	Compliance Program Guidance Manual (CPGM 7356.002 titled "Drug Manufacturing Inspections"	1 February 2002	www.fda.gov	Internal FDA document which delineates how FDA employees are to inspect drug manufacturing facilities using Quality Systems Based approach. Draft implementation occurred in 2000 formal acceptance occurred in 2002.
A13	RE: Digoxin Tablets 0.25 mg Amide Complaint # C04-016 Mylan Complaint # 2004S100417	8 June 2004	Plaintiff's Exhibit 241	Letter to Amin Nanji, Rite Aide Pharmacy #5238 220 36th Street Bellingham, WA 98222. In reference to inquiry regarding thick Digoxin Tablet. Please return sample for investigation, letter.
A14	Amide Pharmaceutical, Inc. Investigation Final Report for Digoxin Tablet, 0.25 mg Control No. 3611A Investigation No. 04-003	9 July 2004	Plaintiff's Exhibit 128	Investigation Summary on thick Digoxin tablet: <ul style="list-style-type: none"> • 5.71 mm thick <ul style="list-style-type: none"> ◦ Specifications are 2.7 mm – 3.7 mm • Weight 0.272 grams <ul style="list-style-type: none"> ◦ Specifications 0.114 – 0.126 • Definitive cause was not identified, guesses put forth • Compression occurred on machines #67 and #71 • Compression occurred 6,7 and 10 November 2003
A15	Amide Pharmaceutical, Inc. Investigation Final Report for Digoxin Tablet, 0.25 mg Control No. 3611A Investigation No. 04-003:	13 July 2004	Plaintiff's Exhibit 242	Conclusions with respect to thick tablet investigation: <ul style="list-style-type: none"> • Tablet was thicker than normal • Tablet may have been produced at setup of compression machine

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	Final Letter Mr. Amin Nanji Pharmacist			<ul style="list-style-type: none"> Isolated incident NOTE: No chemical testing performed to determine potency
A16	FDA Form 483 for Inspection Held 10 January to 8 February 2006	8 February 2006	ACTAV000028901	FDA reported the following in 8 observations: <ul style="list-style-type: none"> Adverse drug experiences not reported to FDA within proper time frame or not reported at all, including Death Associated with Digitek on 9 May 2000 2.5 hours after taking Digitek No review of literature related ADE for products No written procedures for ADEs Failure to investigate consumer complaints including a metal screw found in a bottle of product by a patient. Failure to investigate OOS percent yield of bulk material No process validation Qualification and start-up procedures in manufacturing is inadequate
A17	Amide Pharmaceutical, Inc. Company Response by Jasmine Shah, Vice President of Regulatory Affairs and Quality Compliance to FDA	28 February 2006	Plaintiff's Exhibit 230	Amide acknowledges deficiencies in all cases and pledges to implement appropriate corrective actions including review of documentation, reporting results to FDA all revisions of SOPs as appropriate. States:

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	Form 483 for Inspection Held 10 January to 8 February 2006, Little Falls, NJ			"We have taken the appropriate actions to correct deficiencies and have implemented procedures to preclude their recurrence wherever possible. We have responded to these Inspectional Observations in a prompt and positive manner, and we commit ourselves to a continuing review of all products and procedures to assure compliance with regulations."
A18	Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa LLC Inspection Conducted 10 July to 10 Aug 2006, Little Falls, NJ	After 10 Aug 2006	Plaintiff's Exhibit 90	<p>This report was issued following an inspection conducted by FDA starting from 10 July 2006 to 10 August 2006. This inspection was a general GMP inspection as well as a pre-approval inspection for certain [redacted] products. This inspection was afforded through Compliance Program Guidance Manual CPGM 7356.002: Drug Manufacturing Inspection and 7346.832 Pre-Approval Inspections/Investigations. Inspectional coverage including the Quality, Laboratory Control and Materials System.</p> <p>FDA's overall assessment:</p> <ul style="list-style-type: none"> • "A review of the firm's manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented". <p>There were 15 Observations cited in the Form 483 which was issued for the inspection. These included:</p>

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				<ul style="list-style-type: none"> • 1-The Quality Unit lacks authority to fully investigate errors that have occurred. • 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing • 3- The responsibilities and procedures applicable to the quality control unit are not fully followed • 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications • 5- Input to and output from the computer are not checked for accuracy • 6- The suitability of testing methods is not verified under actual conditions of use • 7- The written stability testing program is not followed • 8- Examination of testing samples is not done to assure that in-process materials conform to specifications • 9- Deviations from written procedures and process control procedures are not recorded and justified • 10- Master production and control records are deficient in that they do not include complete sampling and procedures • 11- Equipment used in the manufacture, processing, packing, or holding of drug products is not of

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				<p>appropriate design to facilitate operations for intended use</p> <ul style="list-style-type: none"> • 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product • 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable • 14- Written procedures are not followed by receipt and storage of components • 15- There was a failure to handle and store components at all times in a manner to prevent contamination <p>Divya Patel is often cited as the most responsible person at the Little Falls Facility.</p>
A19	Warning Letter 06-NWJ-15 to Divya Patel, President Actavis Totowa, LLC Little Falls New Jersey	15 August 2006	Plaintiff's Exhibit 229	<p>This Warning Letter 06-NWJ-15 was issued following a 10 January to 10 February 2006 Inspection of the Little Falls New Jersey site. The following compliance issues were raised by FDA:</p> <ul style="list-style-type: none"> • Failure to submit six potentially serious and unexpected adverse events dating back to 1999 for products such as Digoxin that were not reported to

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				<p>FDA</p> <ul style="list-style-type: none"> • Serious and unexpected ADE reports were not promptly investigated • Failed to adequately review ADE information as required by law • Never filed periodic safety report as required by law • Procedures for surveillance, receipt, evaluation, and reporting of adverse events have not been submitted as required by law.
A20	Response to Warning Letter 06-NWJ-15 by Divya Patel, President Amide Pharmaceutical, Inc. Little Falls New Jersey	6 September 2006	ACTAV000028929	<p>Response states "After reviewing our responses to the form FDA 483 presented to us on February 8 2006 we must acknowledge that we did not provide a comprehensive evaluation of how Amide has administered its Adverse Drug Experience ("ADE") program from 1999 into February or a full description of the changes made to assure future compliance."</p>
A21	Actavis Totowa, LLC Response to FDA Form 483 Observations as a Result Inspection of Amide Pharmaceuticals, Inc. Inspection Conducted 10 July to 10 Aug 2006 Little Falls, NJ	29 August 2006	ACTAV0000511447	<p>Companies response to Form 483 Observations is as follows:</p> <ul style="list-style-type: none"> • 1-The Quality Unit lacks authority to fully investigate errors that have occurred. Amide disagrees with FDA, however agrees with others and "....that some observations made in this inspection indicate that the quality unit has failed

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				<p>to assure that all systems, for example, laboratory documentation and preventive maintenance are administered optimally". However, Amide feels that "... the bottom line is that the systems have been and are sufficient to assure product quality".</p> <ul style="list-style-type: none"> • 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing. Modified DOI, analyst re-trained on modified procedures and on laboratory documentation in general. Company states "We shall be attentive to assuring this instruction is observed". Semi-annual audits of laboratory notebooks to conduct to evaluate conformance with CGMPs. • 3- The responsibilities and procedures applicable to the quality control unit are not fully followed. Tacit agreement to many aspects with some push back on specifics. New SOPs created and personnel trained. • 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications. Reported consultant recommended the QC Director implementing that laboratory errors be more extensively documented. • 5- Input to and output from the computer are not

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				<p>checked for accuracy. Observation recognized as correct.</p> <ul style="list-style-type: none"> • 6- The suitability of testing methods is not verified under actual conditions of use. Will perform recovery studies for all products missing recovery. • 7- The written stability testing program is not followed. Disagrees with observation and provided data to support. • 8- Examination of testing samples is not done to assure that in-process materials conform to specifications. Observations are correct. Training conducted to address. • 9- Deviations from written procedures and process control procedures are not recorded and justified. Observation is correct. Revised procedures to ensure that unusual observations are documented in the data sheet in the batch record. All personnel receive new training. • 10- Master production and control records are deficient in that they do not include complete sampling and procedures. Observation essentially correct. Revised procedures to ensure all events, decisions, and observations bearing on product quality are documented in the data sheet and elsewhere on the batch record. • 11- Equipment used in the manufacture, processing,

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				<p>packing, or holding of drug products is not of appropriate design to facilitate operations for intended use. Agree to incomplete qualification of equipment (Tablet press Stokes BB2 Equipment ID # 70) Committed to review all re-qualification reports and will write discrepancy report for deviations. NOTE: This is one of two presses involved in Digoxin Double Thick Tablet Production</p> <ul style="list-style-type: none"> 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product. Duct tape removed; personnel trained not to make modifications. Procedures written or re-written as needed. 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable. Agree with some, not with others; reviewing, revising and training as necessary. 14- Written procedures are not followed by receipt and storage of components Agree with some, not with others; reviewing, revising and training as necessary. 15- There was a failure to handle and store

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				<p>components at all times in a manner to prevent contamination Agree with most points. Refresher training as necessary.</p> <p>NOTE: Broad statement "Notwithstanding that in our judgment, the facts show Actavis Totowa exercises adequate control through its quality unit, we recognize that the company confronts considerable opportunity for improvement."</p> <p>NOTE ON BIG PICTURE: Responses are to specific questions and solutions are band aids. No Systems Based Solutions are being proposed or implemented.</p>
A22	Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations	September 2006	www.fda.gov	Guidance is intended to help manufacturers implementing modern quality systems and risk management approached to meet the requirements of 21 CFR parts 210 and 211. The guidance is not intended to place new expectations, or replace CGMP requirements to assist in their compliance.
A23	Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa LLC Inspection Conducted 18 September to 11 October 2006 Taft Road, Totowa, NJ	17 November 2006 (Cover Date)	ACTAV00002934	This report was issued following an inspection conducted by FDA starting from 18 September to 11 October 2007. This inspection was of the packaging, labeling and testing facility conducted under Special Audit Assignment. A General GMP inspection was also conducted. There were 3 Observations cited in the Form 483 which was issued for the inspection. These included:

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				<ul style="list-style-type: none"> • 1- Deviations from written specifications, test procedures and laboratory mechanisms are not justified • 2- The accuracy, sensitivity and reproducibility of test methods have not been established • 3- Verification of the suitability of the testing methods is deficient in that they are not performed under actual conditions of use.
A24	e-mail from John Deiriggi to Hal Korman Fw: Actavis-Digitek	4 January 2007	Plaintiff's Exhibit M21	<p>"I believe that we should seriously consider looking at either manufacturing the product here as an alternate site to Amide."</p> <p>NOTE: This is in response to Walter H. Owens Senior Vice President R&D Chemistry Mylan Pharmaceuticals, Inc. who states in the e-mail chain "Overall I am concerned with the long-term viability of Amide, either through quality issues or contract issues. The next course of action being taken is that Joe Duda's group and Legal will be contacting Actavis to try and get clarity as to what they want to do with the contract."</p>
A25	Warning Letter 07-NWJ-06 to Divya Patel, President Actavis Totowa, LLC Little	1 February 2007	Plaintiff's Exhibit 25	<p>This Warning Letter was issued following a 10 July to 10 August 2006 Inspection of the Little Falls New Jersey site. The following compliance issues were raised by</p>

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	Falls New Jersey			<p>FDA:</p> <ul style="list-style-type: none"> • Significant deficiencies in Quality Unit • Laboratory notebooks don't include all raw test data and don't always document preparation and testing of samples and don't record OOS test results when obtained • Failure to check computer output and input • Failure to recognize when in-process specifications not met or not documented when discovered • No procedures for conducting bulk holding time studies • Failure to identify and control rejected in-process materials to prevent use in manufacturing • Unsatisfactory cleaning validation studies • Differences between Master and Batch Production records • Equipment used in manufacture not adequately qualified. • Failure to establish written procedures for maintenance of manufacturing equipment <p>FDA was not convinced that promised efforts address the quality of the drugs already released to market and requests a third-party audit.</p>
A26	Internal Document "The 302	22 May	ACTA V001420149	Internal project management sheet shows Digoxin lot

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	Sample Batches with Questions Manufacturing Review"	2007		5453A which may have been manufactured in 2005 shows "Tablet OOS for weight on the QA Over Check Data Sheet" indicating continued problems with Digoxin tablet weight variability.
A27	Digoxin Tablets, USP 0.25 mg Annual Product Review January 1 2006 to December 31 2006	3 April 2007	Plaintiff's Exhibit 253	<p>This annual product review had the following findings:</p> <ul style="list-style-type: none"> • 44 batches manufactured for a total of 184,800,000 total tablets • 17 Adverse events were noted including some for <ul style="list-style-type: none"> ◦ Atrial fibrillation ◦ Elevated Digoxin level in blood ◦ Orthostatic hypotension ◦ "Unknown" potency question • Detail of investigations was limited due to inability to trace product in market to lots produced at plant • One lot, 60319A Final Blend Assay Standard Deviation was 4.5% which was higher than other batches • Some additional Content Uniformity and Dissolution values were "slightly higher" compared to other batches reviewed.
A28	UDL Laboratories, Inc. Receiving Inspection Form for receipt of 0.25 mg Digitek Tablets	28 June 2007	Plaintiff's Exhibit M65	<p>Notes that "4 tabs out of UDL's thickness tolerance".</p> <p>NOTE: UDL has tighter specifications on thickness than Actavis because of blister packaging needs.</p>

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A29	Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa LLC Inspection Conducted 5 September to 28 September 2007 Little Falls, NJ	5 September to 28 September 2007	Plaintiff's Exhibit 158	<p>This report was issued following an inspection conducted by FDA starting from 5 September to 28 September 2007. This inspection was conducted as a follow-up to Warning Letter # 07-NWJ-06. The inspection provided general GMP coverage as well as pre-approval coverage to one product. Inspection guidance afforded through CPGM 7356.002 and CPGM 7346.832. There were 3 Observations cited in the Form 483 which was issued for the inspection. These included:</p> <ul style="list-style-type: none"> • An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning failure of one or more distributed batches of drug to meet the specifications established for it in the application (stability failure) • Written stability testing program is not followed (36 month pull not tested for four products) • Written production and process control procedures are not followed in the execution of production and process control functions (DOP #0033 Investigations of Out of Specification Results and DOI # QC-059 are not followed)
A30	e-mail 1 October 2007 From Sarita Thapar to Saira Rizvi	1 October 2007	Plaintiff's Exhibit 249	E-mail lists "...top 3 products with AER's associated with death or permanent injury..." Last years answer

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	Regarding Insurance Questions			[2006] Digoxin 0.25 mg.
A31	Incident Report for Digoxin 0.125 mg Control # 70924A1	30 November 2007	Plaintiff's Exhibit 44	<p>Two tablets of Digoxin tablets 0.125 mg were found with approximately double the thickness from counter channels during packaging/filling operation on packaging line #405. Individuals present or included on investigation were:</p> <ul style="list-style-type: none"> • Vilas Patel (line lead person) • Dilip Joshi (packaging manager) • Ashesh Dave (director of packaging) • Aida Ruiz (QA supervisor) • Dan Bitler (QA director) <p>Although initially halted, production continued under "a watchful eye" following a visual only inspection</p>
A32	Investigation of Deviation Report: Digoxin Tablets 0.125 mg (145), Investigation Log No. 07-093 Product Lot No. 70924A1	5 December 2007	Plaintiff's Exhibit 16	<p>Description of Problem: Two tablets of Digoxin tablets 0.125 mg were found with approximately double the thickness from counter channels during packaging and filling operation. No root cause determined. Batch 709242A1 put on hold by QA. Deviation is considered an isolated incident; therefore no other batches are impacted.</p> <p>No Chemical Testing was Conducted.</p>

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
A33	Memorandum from Li Radtke to Executive Staff at UDL Laboratories, Inc. Regarding Actavis Totowa Re-Assessment Summary	21 January 2008	Plaintiff's Exhibit M45	<p>Delineates recalls of products:</p> <ul style="list-style-type: none"> • August 10, 1995 Incorrect package insert • December 1990 Variation in tablet size resulting in sub- and super-potency.
A34	Digoxin Blend Failure Investigation	Unknown. (Probably last quarter 2007)	Plaintiff's Exhibit 159	<p>Notes increase in blend analysis failures from sampling changes. Lots include 70148A and 70207A. Potential causes:</p> <ul style="list-style-type: none"> • Blend sampling procedures (change over to slugs) • Low humidity/high sampling • API particle size • Batch record problems • Method issues • Product validation • Laboratory testing <p>Relative humidity levels were noticed to be lower for months of October through April. Dryer conditions may lead to electrostatic attractions which may be the cause for the higher number of blend failures.</p> <p>Blend was subject to additional testing, which it passed, and released.</p>

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A35	URGENT: DRUG RECALL Digitek (Digoxin tablets, USP) from Actavis to Valued Customer	24 April 2008	Plaintiff's Exhibit 113	States "This recall notice has been initiated due to overweight tablets. Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be observed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy."
A36	UDL Internal Investigation Record from Digitek Tablets, .125 mg and .250 mg	15 May 2008	Plaintiff's Exhibit M69	Investigation summary states "...One complaint for Digitek 125 mcg (#08-038) reported that the customer observed that the tablets appear smaller than usual and that her heart starting racing. This complaint was forwarded to PSRM on 3/18/08 for investigation and it remains open." NOTE: This complaint was before any recall notice.
A37	Establishment Inspection Report (EIR) for FDA Inspection of Actavis Totowa	After 20 May 2008	Plaintiff's Exhibit 91	This report was issued following an inspection conducted by FDA starting from 18 March 2008 to 20 May 2008. This inspection was conducted as a

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	LLC Inspection Conducted 18 March to 20 May 2008 Riverview New Jersey			<p>qualifying GMP inspection for the new Riverview facility. The inspection provided general GMP coverage. Pre-approval coverage was not planned or conducted. Inspection guidance afforded through CPGM 7356.002 and CPGM 7346.832. There were 11 Observations (with significant detail and example) were cited in the Form 483 which included:</p> <ul style="list-style-type: none"> • 1-The responsibilities and procedures applicable to the quality control unit are not fully followed • 2-Drug products failing to meet established specifications and quality control criteria are not rejected. • 3-There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed • 4-Determinations of conformance to appropriate written specifications for acceptance are deficient for in-process materials • 5-Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identify, strength, quality and purity. • 6-Investigations of an unexplained discrepancy and a

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				<p>failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy</p> <ul style="list-style-type: none"> • 7-An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application. • 8-Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications • 9-Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance. • 10-Changes to written procedures are not reviewed and approved by the quality control unit. • 11-Drug product production and control records are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed
A38	Actavis Totowa, LLC	11 June	ACTAV001302483	These Form 483 observations were specifically

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	Response to FDA by Sigurdur Olafsson, Deputy CEO, Actavis Group, CEO Actavis, Inc. by Form 483 Observations as a Result Inspection of Actavis Totowa Inspection Conducted 18 March to 20 May 2008 Riverview New Jersey	2008		<p>addressed by Sigurdur Olafsson, Deputy CEO, Actavis Group, CEO Actavis, Inc. In the cover letter he makes the statement "It is quite fair to say, as we related ion our April 28, 2008 letter that Actavis Totowa prides itself in maintenance of CGMP compliance by virtue of comprehensive and robust quality systems. Thus we were surprised and chagrined as the last inspection developed by our failure to have secured the compliance we had sought and committed to establish at Actavis Totowa. In recognition of that situation, which we concede is largely reflected in the Form 483 observations listed below, we took the following actions:</p> <ul style="list-style-type: none"> • All product manufacturing and distribution was suspended. • A highly qualified team of consultants from PAREXEL was engaged to assist Actavis Totowa in a complete evaluation of all its quality systems and the Company's products. • With the respect to previously distributed product, PAREXEL is conducting a thorough risk assessment pursuant to a protocol that has been provided to the agency on May 30 2008. • The Company has reduced the number of products in its portfolio and, thus the number of batches that need to be supported by its quality system. • Resumption of manufacturing will entail notice to

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				<p>FDA and be gradual and measured. The Company PAREXEL will conduct comprehensive assessments to determine whether manufacturing can be supported by pertinent qualifications and validations, and whether Procedures adequate for in-process finished product and post-marketing monitoring and controls are in place. Only then will a product be suitable for release and distribution. As may be appropriate, equipment may be re-qualified, and methods and processes revalidated.</p> <ul style="list-style-type: none"> • Until such time as the Company determines that the Company's product release systems are sufficiently robust and reliable, PAREXEL will audit Company release decisions and must concur before product is distributed. • Product currently in warehouses continues to be quarantined. Although the Company had concluded that certain batches were suitable for distribution based on its assessments and risk-based assessments by PAREXEL, and resumed limited distribution for a short period of time, it has suspended that distribution. There are no plans to resume distribution of previously manufactured product. • As part of our restructuring and corrective action initiative, we shall adopt procedures that require that Actavis, Inc. management be regularly informed concerning site Quality Systems and CGMP

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				<p>compliance.</p> <ul style="list-style-type: none"> Actavis Totowa has filed reports with the agency on a regular basis to provide updated information. We shall continue to do so, with the minor modification that such updates will henceforth be monthly, rather than weekly to more efficiently capture material developments. <p>Responses to specific Form 483 observations are generally accepted at face value however; where they are incorrect (e.g. Observations 5 with respect to equipment qualification) are not agreed to.</p>
A39	Investigation # 08-060: Digoxin Tablets 0.125 mg (125) Lot # 80228A1 1 April 2008	1 April 2008	Plaintiff's Exhibit 141	Overweight tablets were found during packaging. Preliminary investigation showed a 5000 count bottle had 17 out of 30 tablets above 120 mg. Put on hold pending QA investigation.
A40	Health Hazard Evaluation – Digoxin Tabs 01.25 mg	18 April 2008	Plaintiff's Exhibit 220	Concludes double thick tablets could lead to digitalis toxicity. Can result in death. Thin tablets may cause congestive heart failure and arrhythmia.
A41	e-mail from Wanda Eng to Phyllis Lambridis Regarding Potential 483 items.	17 April 2008	Plaintiff's Exhibit 146	Detailed list of potential 483 items. NOTE: Ms. Eng during deposition claims that these were not specific observations related to the company but based on her past experience.

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
A42	Establishment Inspection Report (EIR) for FDA Inspection of Actavis Elizabeth LLC Inspection Conducted 21 April to 21 May 2008 Elizabeth New Jersey	6 June 2008 (from 21 April to 21 May)	Plaintiff's Exhibit 80	<p>This inspection was conducted as a follow-up to Warning Letter 06-NWJ-15 which was issued on 15 August 2006. Inspection guidance afforded through CPGM 7356.002 and CPGM 7346.832. Major areas of review included 15-day reports, late reporting, periodic reports, deactivated cases, medical inquiries, lack of effective complaints and written procedures. There were 4 Observations cited in the Form 483 which included:</p> <ul style="list-style-type: none"> • 1- Adverse drug experience information had not been reported to FDA (continuing problem from 2006) • 2-ADE's not reported to FDA in 15-day required time frame which were either serious or unexpected • 3-Failure to send periodic (quarterly) reports to FDA (substantially redacted) within 30 days of the close of the quarter • 4-The flow of in-process materials through the building is not designed to prevent contamination
A43	Actavis Totowa, LLC Response to FDA Form 483 Observations as a Result Inspection of Actavis Totowa Inspection Conducted 21	6 June 2008	ACTAV000028820	<p>Responses to the Form 483 observation are summarized below:</p> <ul style="list-style-type: none"> • 1- Adverse drug experience information had not been reported to FDA (continuing problem from

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	April to 21 May 2008 Elizabeth New Jersey			<p>2006) Agreed to observation Purchase of Alpharma will enhance all reporting</p> <ul style="list-style-type: none"> 2-ADE's not reported in 15-day required time frame to FDA either serious or unexpected. Agreed, working on system. Root cause was non-US events. 3-Failure to send periodic (quarterly) reports to FDA (substantially redacted) within 30 days of the close of the quarter. Agreed, working on system. Root cause was non-US events. 4-The flow of in-process materials through the building is not designed to prevent contamination. Agreed with finding, implementing corrective actions.
A44	e-mail from Howard W. Martin to Tammy Maisel, RE: Actavis Totowa Recall, Good Think UDL pulled these products	21 July 2001	Plaintiff's Exhibit M64	e-mail states "Good thinking, UDL pulled these products and put them aside when Digitek broke". Indicating that Mylan and UDL recognized in advance that the problems related to Digitek were not limited to Digitek and took pre-emptive initiatives.
A45	Complaint for Permanent Injunction United States of America v. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur	14 November 2008	Plaintiff's Exhibit 82	Detailed account of five FDA inspections over last three years (2005 to 2008) Five inspections over three years revealed numerous and reoccurring violations of CGMP requirements examples include:

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	Oli Olafsson, Douglas Boothe			<ul style="list-style-type: none"> • Failed to investigate OOS testing results • QA didn't initiate OOS investigations • Failure to verify suitability of methods • Failure to record and justify deviations from written procedures • Deviated from written procedures and specifications • Test methods didn't work as intended • Failure to follow written stability program • Failure to investigate failed batches
A46	e-mail from Richard Dowling to Bharat Patel Regarding New Punches for Digoxin	18 December 2007	Plaintiff's Exhibit 97	Document states "As part of the corrective action for investigation number 07-093 for Digoxin double tablets, I am going to state that we will buy a complete set of lowers and dies for both strengths of Digoxin that will be dedicated and not used for any other products. It is possible the tablet stuck to the punch and was double compressed".
A47	Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, Douglas Boothe	23 December 2008	Plaintiff's Exhibit 214	Detailed agreement "...establish and document management controls over Quality Assurance (QA) and Quality Control (QC) for the Actavis Totowa Facilities."
A48	Digoxin Tablets, USP 0.125	Draft	Plaintiff's Exhibit	This annual product review had the following findings:

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	mg Annual Product Review January 1 2008 to December 31 2008		144	<ul style="list-style-type: none"> • Manufactured 19 batches and 8 were rejected • Rejection came only after FDA inspection which prompted company to do voluntary recall of the product due to the potential for double thick product on market • 22 ADE/Product complaints were reported
A49	Memorandum from UDL Li Radtke to Executive Staff Regarding Actavis-Totowa Re-Assessment	21 January 2008	Plaintiff's Exhibit M45	<p>Summary of Regulatory Affairs/Compliance's evaluation of Actavis Totowa. Lists following [redacted] recall history:</p> <ul style="list-style-type: none"> • August 10, 1995 Class II recall for incorrect package insert • December 1990 Class II recall for variation in tablet size and resulting in sub and super potency
A50	e-mail From Sigurdur Oli Olafsson to Mark Keatley Regarding Inquiry About Financial Impact of Digitek Problems	2 May 2008	Plaintiff's Exhibit	<p>e-mail was responded to with "I suggest we talk about this - don't put this on e-mail." Financial impact questions include:</p> <ul style="list-style-type: none"> • What is FY 2008 revenue and gross margin for product? • Any deaths or injuries alleged against us? • Are we covered by insurance vs. product/process

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				liability and Mylan liability? <ul style="list-style-type: none"> Estimated recall cost only for this product Need Digitek answers asap
A51	e-mail from Jeffrey Rope to Grudrun S. Eyjolfsson CC: Chris Young Regarding FDA Update	3 May 2008	Plaintiff's Exhibit 227	<p>This e-mail communicates potential upgrades, corrective actions and observations with respect to ongoing FDA actions. Of note are the following:</p> <ul style="list-style-type: none"> Have recommended purchase of 3-4 new PTK [tablet] presses with compaction force weight control and automatic reject. Digoxin presses will be fitted with Kramer de-duster to protect operators from Digoxin tablet dust during packaging. "In my view it is totally unacceptable that our people cannot read English operating procedures and batch records."
A52	e-mail from Suzanna Wolfe to Connie Hatcher, Mylan Pharmaceuticals, Inc. QA Manager, Outsourced Products & QA Compliant Investigations RE: Digitek parameter review	4 January 2008	Plaintiff's Exhibit M14	e-mail states "Connie- 70926A1 and 70953A1 have low assay (96.2 and 97.3%). We are looking for 71004A1."

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
A53	Mylan Internal Memo to File 23 January 2008 Final Corrective Action Memo- Audit XA-06-010. Date of Inspection was 8-9 November 2006	23 January 2008 (8-9 November 2006)	Plaintiff's Exhibit 136	<p>Summary of Mylan CGMP Audit of Actavis Totowa LL, at Little Falls, NJ for Digoxin Tablets 0.125 mg and 0.25 mg. Of note are the following:</p> <ul style="list-style-type: none"> • Audit was originally conducted 8-9 November with report completed 4 December 2006 • States that "There is no Quality Agreement in place with Actavis Totowa LLC • Mylan admits to not conducting an in-depth systems audit but took Vice President of Regulatory and Qualities word for status of compliance with CGMPs and appropriateness of response to FDA • Several statements of "Documents to be provided later". • Digoxin manufactured exclusively for Mylan • Dated equipment noted • Quality Control laboratory area was congested • Warehouse for containers and closures was leaking water form the ventilation system and smelled of mildew upon entering. • Copies of important documents still not provided <ul style="list-style-type: none"> ◦ Actavis response to August 2006 Warning Letter ◦ Summary of Digoxin complaints submitted to FDA ◦ Correspondence with FDA regarding complaints ◦ Periodic updates with FDA regarding QSIP ◦ FDA 483 observations and responses to the

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				September 2006 inspection
A54	e-mail From Misbah Sherwani to unknown individual 15 April 2008 FW: List by Product Attach: 5-Sep-07 Present Investigations by product.xls	15 April 2008	Plaintiff's Exhibit 217	Spreadsheet contains an entry which states: "Operator noticed tablets that were thinner than a typical tablet during inspection of drum #2". Investigation number 08-030 for Lot Number 80133A.
A55	Recall-Firm Press Release on FDA Website: Actavis Totowa (formerly known as Amide Pharmaceutical, Inc.) recalls all lots of Bertek and UDL Laboratories Digitek (Digoxin tablets, USP) as precaution	25 April 2008	www.fda.gov	Class I recall notice. "The voluntary all lot recall is due to the possibility that tablets with double the appropriate thickness may have been commercially released. These tablets may contain twice the approved level of active ingredient than is appropriate".
A56	e-mail from Chuck Koon to Hal Korman regarding Actavis (Amide) Recall and FDA Inspection	27 April 2008	Plaintiff's Exhibit M25	Appropriate excerpts "Well over a year ago, we (Quality) presented a review of the compliance issues at Amide to the outsourced committee that was meeting regularly at this time." "Though Amide was always required to notify us of any FDA actions, not only did they not ever do that but, when we contacted them we got nowhere".

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
				"The outsourced committee was reviewing the language in the 10-year contact to see if there was any "out" for us."
A57	URGENT DRUG RECALL letter for Digoxin by Actavis	28 April 2008	Plaintiff's Exhibit 120	"This recall has been initiated due to overweight tablets." Also states "Death can result for excessive digitalis intake" and "...exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia due to lack of therapeutic efficacy". Customers in this case are pharmacists not patients.
A58	e-mail From Mylan Jennifer Urso to Jill Abraham 30 April 2008 FW Dig recall	FW: 30 April 2008	MYLN000932683	"... CSC reports finding a card of Digoxin with one double thickness tablet at GL-Gloucester. The card had 4 tablets remaining- one of which was she reported as obviously double thickness." "Lynne brought this to my attention as it was reported to some facilities yesterday by pharmacy consultants that their supplies were not affected by this recall....Fortunately, the facility knew otherwise."
A59	e-mail From Mike Adams, Executive Director QA Compliance, Mylan Pharmaceuticals, to a large number of staff members updating status of Digitek	6 May 2008	Plaintiff's Exhibit M30	References a conference call with Quality, PSRM and Actavis to get information update from Actavis. Salient points include: <ul style="list-style-type: none"> • "Actavis is setting up a process for consumers to obtain a blood test (through Quest)"

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	recall			<ul style="list-style-type: none"> • "Actavis has addressed over 2,500 medical questions since April 25 2008" • Total call volume to Stericycle since recall notice 128,768
A60	General Systems Applicable to Oxycodone IR (Attachment A)		ACTAV00126195	<p>This document very clearly defines previous Quality System failures by specific Quality System and delineates how deficiencies are being addressed.</p> <p>NOTE: This is the "After" picture in the quintessential "Before and After" picture scheme.</p>
A61	Response to FDA 483 Issued to Actavis Totowa 20 May 2008	11 June 2008	Document provided by Miller Law Firm	<p>"Thus, we were surprised and chagrined, as the inspection developed by our failure to secure the compliance we had sought and committed to establish at Actavis Totowa"</p> <p>NOTE: Admission of failure.</p>
A62	e-mail from Howard W. Martin to Tammy Maisel regarding Actavis Totowa recall-	21 July 2008	Plaintiff's Exhibit M64	<p>Shows UDL anticipated site wide recalls at Actavis and purposely held product prior to expanded recall announcements.</p>
A63	Recall-Firm Press Release on FDA Website: Actavis Totowa Announces Voluntary Recall at the Retail Level of	1 August 2008	www.fda.gov	Announces 66 product recalls.

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	All Drug Products Manufactured at its Little Falls, New Jersey Facility			
A64	e-mail from Paul Galea to Tony	2 February 2009	Plaintiff's Exhibit 73	QRB (Quality Review Board) Minutes from 26 January 2009. One page titled "Little Falls Product Complaints by Category (August 2008 to January 2009): 9 reports of Double Thickness (Digoxin Tablets).
A65	e-mail from Phyllis Lambridis to Dan Bitler RE: Mylan/Bertek Quality Head	30 April 2008	Plaintiff's Exhibit 140	e-mail states "It is my understanding that Robert and Siggi have committed to stop producing Digoxin until we have tableting equipment with weight controls. Please do not have any conversations with customers unless you have the full story."
A66	e-mail from Wanda Eng to Apurva Patel Subject: Blend Failure locations	20 July 2007	Plaintiff's Exhibit 140	Points out 19 lots with blend failures (all have OOS numbers). Two lots are for Digoxin Tablets (70148A and 70207A) manufactured on 17 February 2007 and 12 March 2007 respectively. Lot 70148A was rejected after additional testing and lot 70207A was released.
A67	e-mail from Ashok Nigalaye to Bharat Patel Subject: FW: equipment Quote	21 July 2001	Plaintiff's Exhibit 259	An equipment quote #26943 from DLS Enterprises for tablet presses with weight and thickness controls. Other equipment types enclosed in the paper work.
A68	e-mail from Ashok Nigalaye	12 July 2008	Plaintiff's Exhibit	An equipment quote #26943 from DLS Enterprises for

#	Document Title or Description	Creation Date	Exhibit #	Description of Content
	to Divay Patel, CC: Jasmine Shah, Apurva Patel, Bharat Patel Subject: FW: equipment Quote		258	tablet presses with weight and thickness controls. Lead-in e-mail states machines are similar to Stokes BB2s.
A69	Mechanisms, Manifestations and Management of Digoxin Toxicity in the Modern Era	2006	Adis Data Information, BV. Purchased online	Am. J. Cardiovascular Drugs 2006;6(2), 77-86

Attachment B:**Summary of Some FDA Actions Against Amide/Actavis**

#	DATE	FDA ACTIONS	NOTES
B1	28 July to 9 August 1983	<p>FDA Inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Four FDA Form 483 observations following establishment inspection. These include:</p> <ol style="list-style-type: none"> 1. No stability data to support expiration 2. Problems with label control 3. Reconciliation of finished batch granulation with tablet cores 4. Batch records changed without proper study or approval 	<p>This was the very first inspection of Little Falls by FDA following business start up 1 May 1983. Corporate Officers presented to FDA were:</p> <ul style="list-style-type: none"> • Kenneth Kolomer, President • Barry Ballan, Vice President Marketing • Ajit Desai, Vice President Quality Assurance • J.K. Shah, Vice President Production • Bharat Patel, Vice President Compression/Encapsulation <p>NOTE: FDA writes J.K. Shah to have had 12 years experience in tablet/capsule manufacturing when he states in his 26 March 2010 deposition that he had significantly less at this point in operation.</p> <p>NOTE: J.K. Shah states Chandu Patel</p>

#	DATE	FDA ACTIONS	NOTES
			was founder of the company but FDA states Kenneth Kolomer as President in 1983. Bharat Patel has 3 years experience in tableting and encapsulation. Reference: Document retrieved via FOI Services www.foiservices.com
B2	1984-1989	FDA Inspection(s) of Amide Pharmaceutical, Inc. Little Falls New Jersey between September 1984 to March 1989 where significant violations were discovered and documented. Specific problems which led to a Consent Decree were discovered by FDA in 1987 and 1989 inspections. Reference: Within EIR issued Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Conducted 5 to 20 December 1989 and 2 to 15 February 1990 Reference: Jasmine Shah deposition 26 March 2010 p. 120 Reference: Document retrieved via FOI Services www.foiservices.com	
B3	20 April 1989	Voluntary agreement between FDA and Amide Pharmaceuticals to correct GMP deficiencies discovered during previous inspections	Reference cited in summary of findings for EIR dated 12/5-8, 11, 13-15, 19, 20/89 Reference: Document retrieved via FOI Services www.foiservices.com

#	DATE	FDA ACTIONS	NOTES
B4	5 to 20 December 1989 to 15 January 1990	FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey to assess the firms compliance with voluntary agreement dated 20 April 1989. Form 483 issued (6 pages)	Reference: EIR issued Establishment Inspection Report (EIR) for FDA Inspection of Amide Pharmaceutical, Inc. Inspection Reference: Document retrieved via FOI Services
B5	December 1990	Class II product recall for variation in tablet size resulting in sub and super potent drug product	Reference: Plaintiff's Exhibit M45 First Product Recall
B6	Consent Decree of Injunction 92-513, 23 March 1992	"Amide perpetually restrained and enjoined from introducing and delivering for introduction into interstate commerce any article of drug that the defendants have manufactured, processed, packed, tested, or labeled and manufacturing, processing, packing, testing, labeling, holding or doing any other act with respect to any article of drug while such drug is held for sale after one or more of its components have been shipped in interstate commerce, unless and until;"	Specific points under Consent Decree include: <ul style="list-style-type: none"> • QA personnel inadequate in number and have background, education, training, experience or combination therein • QC laboratory personnel inadequate in number and don't have background, education, training, experience or combination therein • Not all laboratory and analytical procedures validated • Laboratory practices don't reflect actual written SOPs and be followed

#	DATE	FDA ACTIONS	NOTES
			<ul style="list-style-type: none"> Records required by GMPs not kept and recorded at the time events occurred Validations need to be reviewed by third party Laboratory instrument procedures need to be reviewed by third party Laboratory analyst need be trained by third party for each type of instrumentation Manufacturing methods, facilities and controls to be need to be reviewed by a third party All products need to be certified by third party
			Reference: Document retrieved via FOI Services www.foiservices.com
B7	12 December 1992 to 27 January 1993	First FDA inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey conducted following Consent Decree. Form 483 issued.	Reference: Plaintiff's Exhibit 235
B8	9 to 17 March 1993	FDA follow-up inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey conducted to review previous inspection commitments. Form 483 issued.	Reference: Plaintiff's Exhibit 235
B9	9 March to 17	FDA inspection conducted. Form 483 issued	Reference: Plaintiff's Exhibit 235

#	DATE	FDA ACTIONS	NOTES
	March 1994		
B10	14 February to 16 March 1995	FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued. FDA specifically cites errors in dissolution testing procedures for Digoxin tablets.	This was an inspection for Digoxin Batch Certification. Digoxin production started after this inspection Reference: Plaintiff's Exhibit 235
B11	8 June 1995	FDA issues batch certification to Amide for authorization to sell Digoxin under the Batch Certification Regulation 21 CFR 310.500.	Reference: Plaintiff's Exhibit 235
B12	10 August 1995	Class III product recall for incorrect package insert	Reference: Plaintiff's Exhibit M45 Second Product Recall
B13	23 April 1996	FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued.	Reference: Plaintiff's Exhibit 235
B14	12 July 1996	Amide requests FDA lift Consent Decree, FDA does not grant request	First request to lift Decree Reference: Plaintiff's Exhibit 235
B15	25 October 1996	FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey at request of Amide in an attempt to lift Consent Decree. FDA denies request and issues Form 483.	Second request to lift Decree Reference: Plaintiff's Exhibit 235

#	DATE	FDA ACTIONS	NOTES
B16	4 November 1996 to 1 December 1997	FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey in an attempt to lift Consent Decree. FDA denies request and issues Form 483.	<p>Third request to lift Decree</p> <p>Extensive GMP issues still existed during this inspection. Form 483 observations were in 21 parts.</p> <p>"The current inspection revealed several GMP deficiencies which include incomplete impurity profile testing on finished product, failure to identify all known starting impurities, and inadequate cleaning validation for all ANDA's. In addition, the firm lacked the following: a written SOP detailing water sampling procedures; validation data to justify hardness specifications; an audit trail for HPLC data collection and entry; an adequate calibration and maintenance program to assure that critical parameters are within acceptable limits for the HPLC system; stability data to support the expiry on in-house standards; formal written investigations for all validation deviations; and environmental monitoring devices in storage warehouses. The firm's QC laboratory notebook data revealed that on several occasions, the analysts reinjected a solution or reanalyzed a</p>

#	DATE	FDA ACTIONS	NOTES
			chromatogram with no justification or explanation; also the firm's use of SOP #030, Alternate Manufacturing Procedure, is inadequate in that the firm could not clearly define the difference between PDR (Planned Deviation Report) and an EDR (Emergency Deviation Report). The use of SOP #033, Product Related Investigations, is inadequate in that the initial date for investigations is not documented or recorded. And that there is no timeframe for when an investigation should be completed. The use of DOI QA #022, Rejecting an Item, is inadequate in that the procedures are not representative of the actual steps for product destruction. Additionally, the firm cannot track the In-Process and Finished Product Rejection Reports to the actual destruction manifests."
			Reference: Plaintiff's Exhibit 235
			Reference: Document retrieved via FOI Services www.foiservices.com
B17	2 April 1998	FDA inspection conducted of Amide Pharmaceutical, Inc. Little Falls New Jersey for sample inspection. Form	Reference: Plaintiff's Exhibit 235

#	DATE	FDA ACTIONS	NOTES
		483 issued.	
B18	2 December 1998 to 8 January 1999	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued. Amide request lifting of Consent Decree but FDA denies request.	Fourth request to lift Decree Reference: Plaintiff's Exhibit 235
B19	29 November to 8 December 1999	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued	Reference: Plaintiff's Exhibit 235 Reference: Plaintiff's Exhibit 233
B20	23 December 1999	Amide receives Digoxin Tablets ANDA approval	Reference: Plaintiff's Exhibit 235
B21	8 to 23 May 2000	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued	Reference: Plaintiff's Exhibit 235
B22	29 October to 29 November 2001	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued	Reference: Plaintiff's Exhibit 235
B23	10 June 2002	Amide released from terms of Consent Decree 10 years after document was signed.	Reference: Plaintiff's Exhibit 235
B24	11 October	FDA issues Warning Letter to Mr. Chandu Patel, Amide	Reference: Plaintiff's Exhibit 233

#	DATE	FDA ACTIONS	NOTES
	2002	Pharmaceutical, Inc. Little Falls, New Jersey	Reference: www.fda.gov First Warning Letter
B25	24 March to 25 April 2003	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued	Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services www.foiservices.com
B26	14 to 25 April 2003	FDA conducted inspection at Taft Road, Totowa, New Jersey. Form 483 issued	Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services Reference: Plaintiff's Exhibit 233
B27	12 to 21 August 2003	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued	Reference: Plaintiff's Exhibit 235 Reference: Document retrieved via FOI Services Reference: Plaintiff's Exhibit 233
B28	15 November to 1 December 2004	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Form 483 issued	Reference: Document retrieved via FOI Services Reference: Plaintiff's Exhibit 233

#	DATE	FDA ACTIONS	NOTES
B29	31 May to 7 June 2005	FDA conducted inspection of Amide Pharmaceutical, Inc. Little Falls New Jersey. Warning Letter issued	Reference: Document retrieved via FOI Services Second Warning Letter
B30	10 January to 8 February 2006	FDA conducted inspection of Amide Pharmaceuticals, Inc. Little Falls New Jersey. Form 483 issued	Reference: Document retrieved via FOI Services Plaintiff's Exhibit 79
B31	1 February to 6 March 2006	FDA conducted inspection of Actavis Pharmaceuticals, LLC/Purepac Elizabeth New Jersey. Form 483 issued	Reference: Document retrieved via FOI Services
B32	10 July to 10 August 2006	FDA conducted inspection of Actavis Totowa, LLC Little Falls New Jersey. Form 483 issued	Reference: Document retrieved via FOI Services Plaintiff's Exhibit 68, 90, 52
B33	15 August 2006	FDA Issues Warning Letter in response to January-February 2006 inspection	Reference: Plaintiff's Exhibit 229, 233, 246 Reference: www.fda.gov Third Warning Letter
B34	18 September to 11 October	FDA conducted inspection of Actavis Totowa, LLC, Totowa New Jersey, Taft Road. Form 483 issued	Reference: Document retrieved via FOI Services www.foiservices.com

#	DATE	FDA ACTIONS	NOTES
	2006		Plaintiff's Exhibit 228
B35	13 December 2006 to 29 January 2007	FDA conducted inspection of Actavis Elizabeth, LLC, Elizabeth, New Jersey. Form 483 issued	Reference: Document retrieved via FOI Services www.foiservices.com
B36	9 January 2007	FDA Issues Warning Letter to Divya Patel, Actavis Totowa, LLC	Reference: www.fda.gov Plaintiff's Exhibit 231 Fourth Warning Letter
B37	1 February 2007	FDA Issues Warning Letter to Divya Patel, Actavis Totowa, LLC	Reference: www.fda.gov Plaintiff's Exhibit 2 Fifth Warning Letter
B38	5 to 28 September 2007	FDA conducted inspection of Actavis Totowa, LLC, Little Falls, New Jersey, Form 483 issued	Reference: Document retrieved via FOI Services Plaintiff's Exhibit 50, 157, 158, 171
B39	18 March to 20 May 2008	FDA conducted inspection of Actavis Totowa, Riverview Dr, Totowa, New Jersey, Form 483 issued	Reference: Document retrieved via FOI Services Plaintiff's Exhibit 91

#	DATE	FDA ACTIONS	NOTES
B40	21 April to 21 May 2008	FDA conducted inspection of Actavis Elizabeth, Elizabeth New Jersey, Form 483 issued	Reference: Document retrieved via FOI Services
B41	25 April 2008	Voluntary recall of all Digoxin tablets agreed to with FDA.	Reference: www.fda.gov Third Recall
B42	24 to 27 June 2008	FDA conducted inspection of Actavis Mid-Atlantic, Owings Mills, Maryland, Form 483 issued	Reference: Document retrieved via FOI Services
B43	1 August 2008	Voluntary recall of all products manufactured at Little Falls, NJ site agreed to with FDA.	Total of 66 products recalled. Reference: www.fda.gov Fourth Recall
B44	14 November 2008	Complaint for Permanent Injunction United States of America v. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, Douglas Boothe	Reference: Plaintiff's Exhibit 82
B45	23 December 2008	Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, Douglas Boothe	Reference: Plaintiff's Exhibit 214

#	DATE	FDA ACTIONS	NOTES
B46	20 February to 31 March 2009	FDA conducted inspection of Actavis Totowa, Little Falls, New Jersey, Form 483 issued	Reference: Document retrieved via FOI Services www.foiservices.com
B47	18 February 2010	FDA Issues Warning Letter to Douglas Boothe, Actavis US, Morristown, New Jersey	Reference: www.fda.gov Sixth Warning Letter

1983 to 2010 (27 Years)

Event	Number	Notes
Number of Form 483s=	26	First Form 483 issued in 1983; Last Form 483 Last in 2009. Most have numerous observations
Number of Warning Letters =	6	
Number of Consent Decrees =	2	
Number of Refusals by FDA to Lift First Consent Decree =	3	
Number of Product Recalls =	4	1990 Class II: Super or sub potent tablets due to thickness 1995 Class III: Incorrect package insert

Event		Number	Notes	
			2008 25 April, Class I Digoxin double thick or super potent	
			2008 1 August, total product recall from Actavis Totowa	
			Little Falls , New Jersey Site, 66 products total	

Appendix C:

Some Historical Facts Regarding Digitek Tablet Manufacturing: Approximate Chronological Order

1. Digoxin has been used as a heart drug for over 230 years. Digoxin tablets have been on the market in the United States since 1938. (Reference: See Attachment A69)
2. Digoxin has a narrow therapeutic index which means that a very narrow range of concentration in the bloodstream must be maintained or toxicity or lack of effect can occur. (Reference: See Attachment A69)
3. Difficulty in manufacture of Digoxin tablets has been known for some time and a concern to FDA early on. This fact prompted Congress to pass the Digoxin Regulation in 1974 (21 CFR Part 310.500) which required manufacturers of Digoxin tablets to submit their products to FDA for certification. (Reference: See Attachment A10)
4. June 1995 FDA issues certification to Amide Pharmaceuticals allowing them to manufacturer and sell Digoxin under the Batch Certification Regulation 21 CFR 310.500. (Reference: See Attachment B11)
5. Continued product safety concerns by FDA prompted the repeal of 21 CFR 300.15, thus requiring the submission of an NDA by the product innovator Burroughs-Wellcome, which was approved in 1995 with the trade name Lanoxin. (Reference: See Attachment A10)
6. During the same period, Amide executed an extensive year long product development effort to formulate, manufacture and collect data to support submission of an ANDA for Digoxin tablets, thus confirming the concern FDA has with respect to the difficulties associated with manufacturing Digoxin tablets. Amides efforts resulted in at least 40 to 50 experiments before the proper formulation was achieved. (Reference: See Attachment A7)
7. Process validation which was included in the ANDA application for Digoxin tablets occurred in mid-November 1997. Process validation did not include all strengths of the product. Process validation was performed only on 0.250 mg strength tablets. The .250 mg tablet is white and does not contain colorant. The 0.125 mg tablet is green and the 0.500 mg tablet is yellow. (Reference: See Attachment A8)
8. Successful formulation of Digoxin tables required micronization during product manufacture. Micronization is the process of transforming active ingredient and/or excipients into a fine powder. Fine powders led to problems with static

electricity during manufacturing especially during the winter months. (Reference: Attachment A7, A34)

9. On 21 February 2001 the Law Firm of McKenna & Cuneo, LLP of Washington DC argued on behalf of Bertek Pharmaceuticals and Amide for revocation of the 1974 Digoxin Regulation (21 CFR Part 310.500) to "...ensure that the marketplace does not include Digoxin tablets that may have disparate bioavailability, unsubstantiated bioequivalence evidence, formulation and manufacturing changes that have not been approved by FDA and unproven labeling claims". (Reference: Attachment A10)
10. Amide first experienced difficulties with FDA from 28 July to 9 August 1983 during its first inspection shortly after the Little Falls, New Jersey facility opened. Major findings included:
 - a. Stability testing program didn't support 2 year expiration
 - b. Control of labels was inadequate
 - c. Personnel making unauthorized changes to batch records
 - d. Unaccounted loss of material during manufacture of tablets

(Reference: Attachment B1)

11. From September 1984 to March 1989 (~5 ½ years) FDA inspections of Amide at Little Falls finds repeated, significant violations of the CGMPs. Major findings include:
 - a. Insufficient methods validation
 - b. Unsound methodology
 - c. Inadequate review of data
 - d. Improper calibration practices
 - e. Poor record keeping
 - f. Lack of submission of periodic reports on ANDA products,
 - g. Insufficient stability data

(Reference: Attachment B1, B2)

12. December 1990 Class II recall initiated for variation in tablet size resulting in sub and super potent drug product, demonstrating lack of manufacturing controls since at least this time. (Reference: Attachment B5)
13. First Consent Decree of Injunction signed by between Chandu Patel, President, Amide Pharmaceutical, Inc. and US Justice Department. Specific points FDA required by include:

- a. QA personnel must be adequate in number and have background, education, training, experience or combination therein
- b. QC (laboratory personnel must be adequate in number and have background, education, training, experience or combination therein
- c. All laboratory and analytical procedures shall be validated
- d. Laboratory practices shall reflect actual written SOPs and be followed
- e. Records required by GMPs shall be kept and recorded at the time events occurred
- f. Validations to be reviewed by third party
- g. Laboratory instrument procedures to be reviewed by third party
- h. Laboratory analyst shall be trained by third party for each type of instrumentation
- i. Manufacturing methods, facilities and controls to be reviewed by a third party
- j. All products to be certified by third party
- k. Third party to certify to FDA all actions have been taken

(Reference: Attachment B6)

14. From 23 March 1992 until 10 June 2002 Amide is frequently inspected by FDA under terms of the Consent Decree and for ANDA Pre-Approval Inspections. FDA writes numerous Form 483s with multiple observations. FDA denies Amide request to lift the Consent Decree on at least three separate occasions. (Reference: Attachment B6-B10, B13-B19, B21-B23)
15. 10 August 1995 Class III product recall initiated by Amide for incorrect package insert. (Reference: Attachment B12)
16. October 1997, Amide submits ANDA to produce Digoxin tablets using process validation data generated in 1994. (Reference: Attachment A8)
17. Amide receives approval from FDA to manufacture and sell Digoxin Tablets on 23 December 1999. (Reference: Attachment B20)
18. 9 May 2000, Adverse Drug Event for Digoxin reported to Amide: Death Occurs 2.5 hours after taking Digitek. Event not reported to FDA. (Reference: Attachment A9)
19. 29 October to 29 November 2001, FDA inspects Amide and makes the following Form 483 observations:
 - a. Thin tablets observed by packaging personnel
 - b. Visual inspection resulted in rejection of 1,600 tablets
 - c. FDA states no assurance that all short weight/thin tablets were rejected
 - d. No written rework procedure in place

- e. No assurances that all 32 stations of tablet press yields tablets within specification for weight or thickness because only 10 of 32 stations were checked during operational/performance qualification studies and compression start-up.

(Reference: Attachment A11)

20. FDA Form 483 Observation for the 29 October to 29 November 2001 states:

“During the packaging of [redacted] thin tablets were observed by packaging personnel. A portion of the batch (drum 4, 7, 8, & 11) was visually inspected for the presence of thin tablets, which resulted in approximately 1,600 tablets being rejected and ultimately the rejection of drums 4, 7, 8 and 11. The entire contents of drum 1,2,3,5,6,9 and 10 were packaged. During packaging, the packaging line was run at slower speed so that thin tablets could be observed on the tracks.

- There is no assurance that all short weight/thin tablets were rejected from the batch
- There was no rework procedure written for the tablet inspection of drums
- During operational/performance qualification studies from compression start-up, 10 & 32 stations of the tablet press are checked for weight and thickness. Therefore, there is no assurance that all 32 stations of the tablet press yield tablets within specifications for weight and thickness”

As part of their response to FDA, Jasmine Shah, Director of Regulatory Affairs states:

“In order to handle this type of problem in the future, Amide has purchased tablet sorting equipment that will sort thick/thin tablets. Enclosed is a purchase order copy for the equipment (Attachment 1). Upon receipt of the equipment, an IQ/OQ/PQ will be performed and the equipment will be used if such a situation arises.”

(Reference: A11, Plaintiff’s Exhibit 236)

- 21. 10 June 2002, FDA lifts first Consent Decree (Reference: Attachment B23)
- 22. 8 June 2004 Amide receives complaint from a pharmacist in Bellingham, WA regarding thick Digoxin tablet. Amide confirms double thickness, no definitive root cause found. Compression occurred on tablet presses #67 or #71. Tablet manufacture occurred 6, 7 and 10 November 2003. No chemical testing conducted on product. This is the first instance of double thick Digoxin tablets reported and confirmed in market place. (Reference: Attachment A13, A14)
- 23. December 2003 Sigurdur Olafsson is made Managing Director of Actavis US. (Reference: p 24, Sigurdur Olafsson deposition 10 February 2010)

24. 16 July 2004 Sigurdur Olafsson begins conducting due diligence review of Amide for potential purchase by Actavis hf. He finds no problems with respect to FDA or compliance with CGMPs. (Reference: Plaintiff's Exhibit 190)
25. Formal due diligence conducted by Actavis for purchase of Amide Pharmaceutical, Inc. from July 2004 to July 2005. According to CEO Sigurdur Olafsson, outside consultants used for detailed due diligence consisting of an operation team and a quality team. No problems with respect to FDA or compliance with CGMPs. (Reference: p 50-52, Sigurdur Olafsson deposition 10 February 2010)
26. Actavis purchases Amide Pharmaceuticals on 27 July 2005. Purchase includes Little Falls Facility (main site), Taft Road Facility and Riverview Facility all within close proximity to one another. Little Falls is the original facility where most of the manufacturing and compliance related difficulties occurred. (Reference: p 24, 225 Divya C. Patel deposition 30 April 2010)
27. 15 May 2006, company named changes from Amide Pharmaceutical, Inc. to Actavis Totowa, LLC following sale to Actavis Group, hf. (Reference: Plaintiff's Exhibit 91)
28. January 2006, Sigurdur Olafsson is made President of Actavis US. (Reference: p 62, Sigurdur Olafsson deposition 10 February 2010)
29. 10 January 2006 to 8 February 2006 FDA inspects Actavis Totowa, Little Falls, New Jersey and writes a Form 483 with 8 observations. Inspection is primarily related to pharmacovigilance. Specifics include:
 - a. Adverse drug experiences not reported to FDA within proper time frame or not reported at all, including Death Associated with Digitek on 9 May 2000 2.5 hours after taking Digitek
 - b. No review of literature related ADE for products
 - c. No written procedures for ADEs
 - d. Failure to investigate consumer complaints including a metal screw found in a bottle of product
 - e. Failure to investigate OOS percent yield of bulk material
 - f. No process validation
 - g. Qualification and start-up procedures in manufacturing is inadequate(Reference: Attachment A16)
30. In e-mails from Ashok Nigalaye to Divya Patel and from Ashok to Bharat Patel dated 12 July 2006 and 21 July 2006. Discussion about purchasing new tablet presses which contain tablet weight and thickness controls, including an

equipment quote #26943 from DLS Enterprises. (Reference: Plaintiff's Exhibit 258 and 259)

31. 10 July to 10 August 2006, FDA inspects Actavis Totowa, LLC Little Falls, New Jersey. Inspectional coverage includes the Quality System, Laboratory Control System and Material System. FDA's summary statement pronounced:

"A review of the firm's manufacturing and laboratory records revealed a lack of assurance that all laboratory and manufacturing deviations are documented."

A Form 483 was issued with 15 observations which included:

- a. 1-The Quality Unit Lacks authority to fully investigate errors that have occurred.
- b. 2-Laboratory records are deficient in that they do not include a complete record of all data obtained during testing
- c. 3- The responsibilities and procedures applicable to the quality control unit are not fully followed
- d. 4- Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications
- e. 5- Input to and output from the computer are not checked for accuracy
- f. 6- The suitability of testing methods is not verified under actual conditions of use
- g. 7- The written stability testing program is not followed
- h. 8- Examination of testing samples is not done to assure that in-process materials conform to specifications
- i. 9- Deviations from written procedures and process control procedures are not recorded and justified
- j. 10- Master production and control records are deficient in that they do not include complete sampling and procedures
- k. 11- Equipment used in the manufacture, processing, packing, or holding of drug products is not of appropriate design to facilitate operations for intended use
- l. 12- Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing or holding of a drug product
- m. 13- Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacture or processing operations for which they are unsuitable
- n. 14- Written procedures are not followed by receipt and storage of components
- o. 15- There was a failure to handle and store components at all times in a manner to prevent contamination

Divya Patel is still the most responsible person on site, Jasmine Shah is still primarily responsible for Quality Assurance and Regulatory Affairs, and Dan

Bitler is still primarily responsible for Quality Assurance approval and sign-off. These observations are similar and consistent with what FDA has found since its first observations starting in 1983.

(Reference: Attachment A18)

32. 15 August 2006 FDA issues Warning Letter to Actavis Totowa, LLC Little Falls New Jersey regarding inspection conducted 10 January 2006 to 8 February 2006. (Reference: Attachment A19)

33. 4 January 2007 Mylan Pharmaceuticals, Inc. openly states reservations about continued relationship with Actavis.

“I believe that we should seriously consider looking at either manufacturing the product here or as an alternate site to Amide”

(Reference: Attachment A24)

34. 1 February 2007, Warning Letter issues to Divya Patel concerning 10 July to 10 August inspection findings. (Reference: Attachment A25)

35. Actavis annual product review for Digitek 0.25 mg tablets on 3 April 2007 for 1 December 2006 to 31 December 2006 finds the following:

- a. 17 Adverse events were noted including some for
 - i. Atrial fibrillation
 - ii. Elevated Digoxin level in blood
 - iii. Orthostatic hypotension
 - iv. “Unknown” potency question
- b. Detail of investigations was limited due to inability to trace product in market to lots produced at plant
- c. One lot, 60319A Final Blend Assay Standard Deviation was 4.5% which was higher than other batches
- d. Some additional Content Uniformity and Dissolution vales were “slightly higher” compared to other batches reviewed.

(Reference: Attachment A27)

36. Blend uniformity failures for different products are discussed in an e-mail from Wanda Eng to Apurva Patel dated 20 July 2007. In particular, Blend Uniformity failures for Digoxin Tablets manufactured on 17 January 2007 and 12 March 2007 are discussed. One lot was rejected after additional testing and one was released. (Reference: Plaintiff's Exhibit 183)

37. 5 September 2007 to 28 September 2007, FDA inspects Actavis Totowa Little Falls, NJ facility as a follow-up to Warning Letter. It is a general GMP inspection and a pre-approval inspection for one product. Summary of findings include:

- a. An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning failure of one or more distributed batches of drug to meet the specifications established for it in the application (stability failure)
- b. Written stability testing program is not followed (36 month pull not tested for four products)
- c. Written production and process control procedures are not followed in the execution of production and process control functions (DOP #0033 Investigations of Out of Specification Results and DOI # QC-059 are not followed)

(Reference: Attachment A29)

38. 1 October 2007 internal e-mail indicates Digoxin 0.25 mg is the top product where Adverse Drug Events are associated with death or permanent injury.
(Reference: Attachment A30)

39. 30 November 2007, Double thick tablets discovered during manufacturing of Digoxin 0.125 mg tablets. Although initially halted, production continued following only visual inspection. Detailed investigation conducted within a very short period of time. Product is released to market without conclusive evidence of what caused the double thick problem on 5 December 2007. No chemical testing of tablets was conducted. (Reference: Attachment A31, A32)

40. Last quarter 2007 Digoxin Blend failure investigation conducted. Potential causes cited include:

- a. Blend sampling procedures (change over to slugs)
- b. Low humidity/high sampling
- c. API particle size
- d. Batch record problems
- e. Method issues
- f. Product validation
- g. Laboratory testing

According to company document, relative humidity levels were lower for months of October through April. Dryer conditions may lead to electrostatic attractions which may be the cause for the higher number of blend failures. (Reference: Attachment A34)

41. In an e-mail dated 18 December 2007, Richard Dowling states to Bharat Patel:

“As part of the corrective action for investigation number 07-093 for Digoxin double tablets, I am going to state that we will buy a complete set of lowers and dies for both strengths of Digoxin that will be dedicated and not used for any other products. It is possible the tablet stuck to the punch and was double compressed”.

(Reference: Plaintiff's Exhibit 97)

42. From 18 March to 20 May 2008 FDA conducted an inspection of the Actavis Totowa new Riverside facility located at 990 Riverview Drive, Totowa, New Jersey. According to the FDA:

“This inspection was limited to coverage of the Quality System due to significant cGMP deficiencies including but not limited to out of specification in-process, finished product and stability results for more than [redacted] prescription pharmaceutical products; release of Digoxin Tablets 0.125 mg, lot# 70924A2, following visual inspection of the [redacted] to remove “double thick” tablets; failure of the Quality Unit to reject products not meeting specifications, to complete Quality Assurance investigations, to expand investigations to other lots and products, to file NDA Field Alerts within timeframes, and to respond to out of specification products on the marketplace. Analytical methods requiring remediation remained in use and approximately [redacted] prescription drug products had no analytical evaluations of impurities on stability. Written procedures were not followed and changes with potential product quality impact were not all reviewed and approved by the Quality Unit. No market action was taken by the Quality Unit for any products on the market at the initiation of the inspection of the inspection despite confirmed out of specification, in-process, finished product and stability results. During the inspection, commitments to recall products were initiated based on inspectional findings. No comprehensive risk assessment or quality evaluation for all products on the market was conducted by the firm's Quality Unit prior to completion of the inspection. No additional systems were covered following the documented Quality System failure.”

“Commitments to recall finished products from the marketplace were initiated on 4/09/08 and continued throughout the inspection for such products as Digoxin Tablets, Pentazocine and Nalaxone Hydrochloride Tablets, Carisoprodol/Aspirin/Codeine Phosphate Tablets, Hydrocodone Bitartrate and Homatropine Methlybromide Tablets and Mult-Bets pediatric prescription vitamins. However, there is no assurance of the strength, quality and purity of the approximately [redacted] of other products that remain on the market, all lots remaining in the two distribution centers, and the in-process products that remain at the firm's Little Falls, NJ and Totowa NJ locations. The products were manufactured, tested and released by the same Quality System”.

(Reference: Attachment A37)

43. Actavis issues urgent recall notice to valued customers stating:

“This recall notice has been initiated due to overweight tablets.”

(Reference: Attachment A35)

44. 25 April 2008 FDA and Actavis announce recall on all Digitek Tablets on the market. (Reference: Attachment B41)

45. On June 11 2008 Sigurdur Olafsson, now Deputy CEO, Actavis Group, CEO Actavis, Inc. issued response to FDA Form 483's generated during the 8 March to 20 May 2008 FDA inspection. He acknowledges most of the observations, but disagrees when he does not believe them to be correct. The following statement best captures his sentiment:

“It is quite fair to say, as we related to our April 2008 letter, that Actavis Totowa prides itself in maintenance of cGMP compliance by virtue of comprehensive and robust quality systems. Thus we were surprised and chagrined, as the last inspection developed, by our failure to have secured the compliance we had sought and committed to establish for Actavis Totowa.”

(Reference: Attachment A61)

46. UDL Internal Investigation Record from March 2008 indicates “...one complaint for Digitek 125 mcg (#08-038) reported that the customer observed that the tablets appear smaller than usual and that her heart started racing”. This observation was made in March before any recall announcement. (Reference: Attachment A36)

47. Actavis Investigation #08-060 for Digoxin Tablets 0.125 mg Lot # 80228A1, 1 April 2008. Overweight tablets were found during packaging. Preliminary investigation showed a 5000 count bottle had 17 out of 30 tablets above 120 mg. Put on hold pending QA investigation. (Reference: Attachment A39)

48. Actavis contracts Health Hazard Evaluation which is issued 18 April 2008. Conclusions:

“Double thick tablets could lead to digitalis toxicity; Can result in death. Thin tablets may cause congestive heart failure and arrhythmia.”

(Reference: Attachment A40)

49. Mylan acknowledges Pharmacist identifying double thick products in market place (Reference: Attachment A58)

50. Actavis begins receiving a substantial number of complaints regarding Digitek (Reference: Attachment A59)
51. The management team responsible for all Operations, Administration and Quality at Amide was essentially the same for Amide since 1989 until 2008. These individuals include:
- a. Chandu Patel-President (~1984 to April 2003, Father of Divya Patel died, referenced within Divya C. Patel deposition 30 April 2010)
 - b. Divya Patel- President (1995 to April 2008, took over as President when father died in April 2003, reference deposition 30 April 2010)
 - c. Ashok Nigayale- R&D (June 1993 to January 2008, reference deposition 31 March 2010)
 - d. Jasmine Shah- Quality and Regulatory Affairs (1988 to August 2008 reference deposition 26 March 2010)
 - e. Dan Bitler- Quality Assurance (1995 to 23 May 2008 reference deposition 22 January 2010)
52. Ashok Nigalaye leaves company January 2008 (Reference: p. 29 deposition 31 March 2010)
53. Divya Patel leaves company April 2008 (Reference: p. 190 deposition of Divya Patel)
54. 27 April 2008 Mylan Chuck Koon in an e-mail to Hal Korman expresses concerns about Actavis problems with compliance being know "Well over a year ago." Also talks about how to get out of 10 year contract. (Reference: Attachment A56)
55. Sigurdur Oli Olafsson and Mark Keatley e-mail exchange on 2 May 2008, begins discussion of financial impact of problems associated with Digoxin production at Little Falls. Points include:
- a. What is FY 2008 revenue and gross margin for product?
 - b. Any deaths or injuries alleged against us?
 - c. Are we covered by insurance vs. product/process liability and Mylan liability?
 - d. Estimated recall cost only for this product
 - e. Need Digitek answers asap
- (Reference: Attachment A50)
56. Jeffrey Rope and Grudrun Eyjolfssdottir e-mail exchange on 3 May 2008 communicates equipment upgrades and concerns related to Digitek production which include:

- a. Have recommended purchase of 3-4 new PTK [tablet] presses with compaction force weight control and automatic reject.
- b. Digoxin presses will be fitted with Kramer de-duster to protect operators from Digoxin tablet dust during packaging.
- c. "In my view it is totally unacceptable that our people cannot read English operating procedures and batch records."

Jeffrey Rope confirms manufacturing people cannot read English and therefore cannot read operating procedures and batch records.

(Reference: Attachment A51)

57. In an e-mail dated 6 May 2008 from Mike Adams, Executive Director QA Compliance Mylan Pharmaceuticals to a large number of staff members, the following points were made with respect to the status of Digitek recall:

- a. "Actavis is setting up a process for consumers to obtain a blood test (through Quest)"
- b. "Actavis has addressed over 2,500 medical questions since April 25 2008"
- c. Total call volume to Stericycle since recall notice 128,768

(Reference: Attachment A59)

58. Actavis indicates plan to purchase new tableting equipment with weight controls
(Reference: Plaintiff's Exhibit 140)

59. Dan Bitler leaves company 23 May 2008 (Reference: p. 16 deposition 22 January 2010)

60. Jasmine Shah leaves company August 2008 (Reference: p.8 deposition 26 March 2010)

61. 1 August 2008 Actavis and FDA announce voluntary recall of all products manufactured at Little Fall, New Jersey facility. (Reference: Attachment B43)

62. 14 November 2008 Complaint for Permanent Injunction United States of America vs. Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe

(Reference: Attachment B44)

63. 23 December 2008 Consent Decree of Permanent Injunction United States of America v Actavis Totowa, LLC, Actavis, Inc. Corporations and Sigurdur Oli Olafsson, and Douglas Boothe.

(Reference: Attachment B45)

Appendix D:
Failure of the Quality System: Examples at Amide/Actavis

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
1983 EIR form Little Falls New Jersey Inspection (A1)	1. No stability data to support 2 year expiry		1. Lack of reconciliation of number of tablet cores after compression 2. Unauthorized changes in batch record			1. Incomplete label inventory
20 April 1989 Voluntary Agreement	1. Inadequate general procedures 2. No procedure to periodically review written procedures 3. Insufficient numbers of staff to support operations 4. No Material Review Board 5. Laboratory audits not performed 6. Inadequate general GMP training	1. Inadequate technical training it laboratory. 2. Laboratory personnel unable to properly use instrumentation 3. No methods validations 4. Inadequate data review	1. Inadequate production procedures 2. Problems with Blend Uniformity 3. Products failing in-process testing			
1989-1990 EIR Little Falls, NJ (A2)	1. Failure to submit periodic reports on ANDA products 2. Inadequate general procedures 3. No procedure to periodically review written procedures 4. Insufficient numbers of staff to support operations 5. No Material Review Board 6. Laboratory Audits not performed	1. Insufficient methods 2. Inadequate technical training it laboratory. 3. Laboratory personnel unable to properly use instrumentation 4. No methods validations 5. Inadequate data review	1. Reuse of parchment paper for drying separate batches of product	1. Inadequate incubator control		

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
1992 Consent Decree (A3)	<ol style="list-style-type: none"> Records required by GMPs and internal SOPs not being kept Personnel don't possess background, education, training and experience Inadequate number of staff 	<ol style="list-style-type: none"> Methods no validated Methods not scientifically valid Laboratory procedures not followed Data not being recorded at time of testing Laboratory personnel not properly trained 				
1994 EIR Little Falls, NJ (A4)	<ol style="list-style-type: none"> QA does not always approve initiation of manufacturing processes. QA releasing batches without review of supporting data packages QA releasing product before process validation reports were written Inadequate manufacturing investigations: No root cause analysis Manufacturing progresses without QA signatures at necessary steps during manufacturing (batch record signatures). 	<ol style="list-style-type: none"> Methods not properly validated Failing test results not investigated Modification of sample methods and testing into compliance will Modified sample preparation at Testing methods for single product did not take different tablet weights into account for analysis and calculation of results 	<ol style="list-style-type: none"> Outside contractor not following procedures and altering them at will. Problems discovered with process validation were ignored Cleaning validation studies not conducted Batch records modified at will during course of production Batch records sometimes "blank forms" filled in during production Not aware of requirement for three batches as part of process validation Failures during process 	<ol style="list-style-type: none"> Use of old and worn out tablet press tooling No maintenance or calibration scheduled for manufacturing equipment including tablet presses and tooling. Inadequate control and sign out of manufacturing tooling. 	<ol style="list-style-type: none"> Use of raw materials from different vendors, not all meeting required specifications Use of material form unapproved vendors in violation of internal SOPs Inadequate controls regarding release of raw material from quarantine 	

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
			<p>validation were ignored.</p> <p>8. No assurance of blend uniformity is attained during process validation and finished product manufacturing</p> <p>9. Particle size distribution problems leading to non-uniform blends</p> <p>10. Modification of acceptance criteria during course of process validation</p> <p>11. Product released to market before process validation reports were written</p> <p>12. Lumps reported in final blend leading to overweight and broken tablets</p> <p>13. Black specs found in blend and tablets, yet no investigations conducted nor procedure in place to address</p> <p>14. Incomplete cleaning validations</p>			
Form 483 Issued 16 March 1995		1. Improper technique during Digoxin dissolution testing				

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
(A5)						
1997 EIR Little Falls, NJ (A6)	<ol style="list-style-type: none"> 1. Failure to follow SOPs for in-process sampling 2. Change control not followed to reflect changes in specifications 3. QA didn't sign off on production records at time of production. 4. Adverse Drug Event reports sent to FDA not recorded or tracked. 5. Customer complaint SOP is inadequate 6. Product related investigations SOP is inadequate: equipment involved not documented; no timeframe for completing 7. Alternate manufacturing SOP inadequate: Planned Deviations and Emergency Deviations ill defined 8. Product reject SOP inadequate 	<ol style="list-style-type: none"> 1. Inadequate methods validation: lack of impurity profile testing for numerous products including Digoxin 2. Failure to identify and test for impurities 3. Use of integrators does not allow review of audit trails. 4. No stability data exist to support reference standard expiration: Digoxin and others 5. Inadequate calibration and maintenance procedures for HPLC systems 6. Reinjection of solutions and reanalysis of chromatograms without justification, explanation or investigation 7. Problems with carryover not properly addressed 8. Data in notebooks don't reflect actual procedures performed at the bench by chemists: steps like sonication and filtration not written down 	<ol style="list-style-type: none"> 1. Inadequate cleaning validation 2. No process validation to support tablet hardness specification 3. Tablet presses operated outside validated range for speed 4. No tablet press speed range tested during process validations 5. No stability data to support tablet drying operations 6. Modification of production steps without justification or supporting studies 7. Manufacturing investigations not conducted when products found to not meet specifications 8. Re-work procedures not approved in advance nor documented when performed. 	<ol style="list-style-type: none"> 1. No SOP for water sampling and testing for water used in manufacturing. 2. No environmental monitoring devices to detect humidity and temperature in: Raw material, in-process storage area, coating rooms, temporary staging hallways 		

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
Form 483 issued from 29 October to 29 November 2001 (A11)			<ol style="list-style-type: none"> 1. No assurance that all short weight/thin tablets were rejected from batch 2. There is no rework procedure written for the tablet inspection of drums 3. No assurance that all tablet press stations are checked during start up tests and thus produce tablets of proper weight and thickness 			
2006 EIR, Little Falls, NJ (A18)	<ol style="list-style-type: none"> 1. No assurance that Quality Unit can be relied upon to fulfill its responsibilities to assure that all drug products released to the marketplace meet the requirements for identity, strength, quality and purity that they purport to have. 2. Batches failing to meet specification released into interstate commerce without full investigations 3. All laboratory data no included with batch records 4. No assurance that Quality Assurance can detect discrepancies in reports for which they are 	<ol style="list-style-type: none"> 1. Laboratory records are deficient in that they do not include a complete record of all data obtained during testing: sample preparations, errors; low yields not documented 2. SOP for OOS investigations not always followed by laboratory personnel; results improperly invalidated 3. Laboratory notebooks not properly maintained; overwrites; changes made after notebook signed off 4. Input to and output from laboratory computers are not 	<ol style="list-style-type: none"> 1. Manufacturing deviations not always documented 2. Cleaning validations not properly performed; equipment might not be clean 3. No assurance that in-process materials meet specifications; proper testing of samples is not performed. 4. Products failing to meet in-process testing specifications are not rejected. 5. No assurance line operators can detect and document out of specification tablets. 	<ol style="list-style-type: none"> 1. Equipment qualifications are not adequate and do not insure the equipment will work as designed and used. 2. Equipment re-qualifications not performed to current industry standards 3. Written 	<ol style="list-style-type: none"> 1. Rejected in-process materials are not identified under an quarantine system to prevent their use in manufacturing or processing for which they are suitable: batches not labeled for reject stored with other materials in the work in 	

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
	<p>responsible</p> <p>5. Written stability testing program not followed; bulk product only-no testing on finished products in all package configurations</p> <p>6. QA inspectors not taking action to reject out of specification products which they discovered during manufacturing</p> <p>7. QA SOPs such as "Routine Tablet Press Overchecks" not being followed</p>	<p>checked for accuracy</p> <p>5. Cleaning methods not properly validated</p>	<p>6. Master production records are deficient and do not include complete sampling procedures.</p> <p>7. Sampling of in-process materials not specifically defined in writing.</p>	<p>procedures are not established and followed for the cleaning and maintenance of equipment including utensils; duct take used for repairs</p>	<p>progress warehouse</p> <p>2. Written procedures are not followed for the receipt and storage of components: components stored and located in unexpected areas; location not listed on inventory cards</p> <p>3. Failure to handle and store components at all times in a manner to prevent contamination; weighing room not cleaned between uses</p>	
2006 EIR 4 Taft Road, Little Falls, NJ (A23)		<p>1. Deviations from written specifications, test procedures and laboratory mechanisms are not justified:</p>	<p>1. Inadequate cleaning validation studies; not test for cleaning agent; no recovery studies</p>			

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
		<p>2. Original values which were failures ignored and retests conducted several times (testing into compliance)</p> <p>3. Investigations not conducted</p> <p>4. Validation studies conducted on the fly- filter studies</p> <p>5. Unknown peaks not identified</p> <p>6. No assurance that methods are appropriate for use due to repeated testing without invalidating original out of specification data obtained during method validations.</p> <p>7. Failures during methods validation were not addressed.</p>				
2007 EIR Little Falls, NJ (A29)	<p>1. NDA Field Alert was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in an application</p>	<p>1. Long gaps exist between testing of samples which initially failed specifications</p> <p>2. Written stability program not followed; product not tested at 36 month stability point</p>	<p>1. SOP for investigation of OOS results not followed as written: investigations not closed within 30 days, interim reports not generated for on going investigations.</p>			
2008 EIR Little Falls, NJ (A38)-	<p>1. The responsibilities and procedures applicable to the quality control unit are not fully</p>					

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
Quality System Review Only (A38)	<p>followed</p> <p>2. Drug products failing to meet established specifications and quality control criteria are not rejected.</p> <p>3. There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed</p> <p>4. Determinations of conformance to appropriate written specifications for acceptance are deficient for in-process materials</p> <p>5. Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identify, strength, quality and purity.</p> <p>6. Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did</p>					

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
	<p>not extend to other batches of the same drug product and other drug products that may be associated with the specific failure or discrepancy</p> <p>7. An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.</p> <p>8. Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications</p> <p>9. Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.</p> <p>10. Changes to written procedures are not reviewed and approved by the quality control unit.</p> <p>11. Drug product production and</p>					

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
	control records are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed					
2008 EIR Elizabeth, NJ (A43)			1. Flow in in-process materials through the building is not designed to prevent contamination			
14 Nov 2008 Complaint of Permanent Injunction	<ol style="list-style-type: none"> 1. Quality Assurance failed to initiate an investigation when there were multiple complaints for the same lot or confirmed contamination complaints 2. Quality Assurance personnel failed to follow written procedures 3. Quality Assurance failed to ensure all data was reviewed 4. Quality Assurance failed to ensure all laboratory deviations were resolved prior to release of drug into commercial distribution 5. Quality Assurance failed to have adequate written procedures 	<ol style="list-style-type: none"> 1. Failure to investigate unexplained OOS testing results 2. Failure to keep complete laboratory records of all testing data 3. Failed to verify the suitability of all testing methods under actual conditions of use 4. Laboratory deviated without written justification, from its own written specifications, test procedures and laboratory mechanisms 5. Laboratory had not established the accuracy, specificity, and 	<ol style="list-style-type: none"> 1. Failure to establish control procedures to validate the performance of manufacturing processes 2. Failure to record and justify deviations from its written production and process control procedures 3. Failure to examine and test examples samples to ensure that in-process materials confirm to specifications 			

Reference	Quality System	Laboratory Control System	Production System	Facilities and Equipment	Materials System	Packaging and Labeling System
	<p>6. Failure to document and investigate failure of drug batches to meet specifications</p> <p>7. Failure to reject drug products failing to meet established standards and specifications and any other relevant quality control criteria.</p>	<p>reproducibility of the test methods that it employed</p> <p>6. Failure to have laboratory controls sufficient to ensure components, in-process materials, and finished drug products have appropriate standards of identity, strength, quality, an purity and conform to their written specifications</p>				